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Review

'Mix and Match' vaccination: Is dengue next?

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ABSTRACT

The severity of the COVID-19 pandemic and the development of multiple SARS-CoV-2 vaccines expedited vaccine 'mix and match' trials in humans and demonstrated the benefits of mixing vaccines that vary in formulation, strength, and immunogenicity. Heterologous sequential vaccination may be an effective approach for protecting against dengue, as this strategy would mimic the natural route to broad dengue protection and may overcome the imbalances in efficacy of the individual leading live attenuated dengue vaccines. Here we review 'mix and match' vaccination trials against SARS-CoV-2, HIV, and dengue virus and discuss the possible advantages and concerns of future heterologous immunization with the leading dengue vaccines. COVID-19 trials suggest that priming with a vaccine that induces strong cellular responses, such as an adenoviral vectored product, followed by heterologous boost may optimize T cell immunity. Moreover, heterologous vaccination may induce superior humoral immunity compared to homologous vaccination when the priming vaccine induces a narrower response than the boost. The HIV trials reported that heterologous vaccination was associated with broadened antigen responses and that the sequence of the vaccines significantly impacts the regimen's immunogenicity and efficacy. In heterologous dengue immunization trials, where at least one dose was with a live attenuated vaccine, all reported equivalent or increased immunogenicity compared to homologous boost, although one study reported increased reactogenicity. The three leading dengue vaccines have been evaluated for safety and efficacy in thousands of study participants but not in combination in heterologous dengue vaccine trials. Various heterologous regimens including different combinations and sequences should be trialed to optimize cellular and humoral immunity and the breadth of the response while limiting reactogenicity. A blossoming field dedicated to more accurate correlates of protection and enhancement will help confirm the safety and efficacy of these strategies.

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1. Introduction

Despite the high morbidity of dengue and > 3 billion people at risk for infection, a universally effective dengue vaccine has eluded scientists for decades [1,2]. The co-circulating and immunologically interactive dengue virus serotypes 1–4 (DENV1-4) pose a unique challenge. Because second infection with a different serotype is associated with severe dengue, all three leading vaccine candidates — Dengvaxia, TAK-003, and TV003 — are tetravalent, live-attenuated, and designed to induce specific immunity against each of the four serotypes simultaneously. However, both vaccines that have completed phase 3 trials have unbalanced efficacy. Dengvaxia induces strong protection against DENV4 and TAK-003 against DENV2, but neither vaccine provides full protection against other serotypes [3–7]. In contrast, TV003 phase 1 and 2 trials indicate that it induces a tetravalent antibody response in about two-thirds of subjects [8–10], but phase 3 efficacy trial results have not been released to date.

Studies of the host response to sequential infection with distinct dengue serotypes and vaccine 'mix and match' trials against other pathogens, including SARS-CoV-2, provide compelling evidence that prime-boost with distinct dengue vaccines (defined here as heterologous vaccination) may overcome the limitations of each vaccine alone. Traditionally, heterologous vaccination has referred to sequential vaccination with different types of vaccines, commonly a viral or DNA vector followed by a protein-based formulation [11]. However, the development of multiple SARS-CoV-2 vaccines, with varying side effect profiles and availability, has expedited the combination of mRNA, viral vector, and protein subunit vaccines. These studies have shown how vaccine formulation, strength, and the sequence of the prime boost may optimize the immune response. Additionally, exposure to different viral strains may induce a more diverse B cell repertoire with prolonged affinity maturation as was observed in a model of human influenza vaccination [12]. Mixing the leading dengue vaccines may harness many potential benefits of heterologous vaccination, including increased immunogenicity and efficacy, by taking advantage of differences in vaccine platforms, parent strains, and order of vaccination.

2. 'Mix and match' COVID-19 vaccinations

'Mix and match' COVID-19 vaccination studies have shown that sequential heterologous vaccination may be more effective than homologous vaccine schedules. These studies were expedited by evidence of vaccine-induced thrombocytopenia and thrombosis associated with AstraZeneca's adenoviral vectored vaccine, ChAdOx1-S-nCoV-19 (ChAd) [13], which prompted European health authorities to suggest that ChAd vaccine recipients may receive a Pfizer/BioNTech BNT162b2 (BNT) vaccine as a second dose [14]. Multiple early observational trials reported that as compared to those who received BNT/BNT or ChAd/ChAd, those vaccinated with ChAd/BNT had higher serum neutralizing titers [15–17], stronger $CD4^+$ and $CD8^+$ T cell responses [18,19], and lower SARS-CoV-2 infection rates [18,20]. However, these studies were limited by differences in the intervals between BNT/BNT dosing (4 weeks) and ChAd prime-boost dosing (~12 weeks).

The Com-COV study group has since performed randomized controlled trials comparing heterologous and homologous COVID-19 vaccination after prime with either BNT or ChAd [21–23]. These have indicated that heterologous vaccination may be particularly effective at bolstering T cell responses, but the sequence and immunogenicity of the vaccines are key to optimizing immunity. Of all the homologous and heterologous sequences assessed, ChAd prime with mRNA boost resulted in the highest T cell responses [21,22]. Atmar *et al.* noted a similar pattern in an observational trial of subjects who had completed a full primary series and underwent homologous vs heterologous boost. In this trial, priming with Janssen's adenovirus-vectored vaccine Ad26.COV2.S (Ad26) with mRNA boost resulted in the strongest cellular responses [24]. When immune responses were tested against variants of concern, neutralizing antibody titers dropped in all groups, but cellular responses remained unchanged [22]. Thus, priming with a vaccine that induces strong cellular responses, such as an adenoviral vectored product, followed by heterologous boost seems to optimize T cell immunity. This may be particularly relevant for protection against emerging variants.

In both the Com-COV and Atmar *et al.* trials, Moderna's mRNA-1273 vaccine induced the highest neutralizing antibody titers regardless of the sequence of vaccination. The other sequences revealed that ChAd/ChAd induced the lowest 50% neutralizing antibody titer (61) followed by BNT/ChAd (383), ChAd/BNT (515) and BNT/BNT (574) [21]. The large difference in binding antibody titers between BNT/ChAd and ChAd/BNT suggests that priming with a stronger vaccine may dampen the immune response to the second, weaker vaccine. Similar observations were made in Com-COV2 where BNT prime followed by Novavax's adjuvanted protein-subunit vaccine, NVX-CoV2373 (NVX), induced lower neutralizing antibody titers than BNT/BNT. In contrast, ChAd/NVX induced 4-fold higher neutralizing antibody titers compared to ChAd/ChAd [22]. In sum, heterologous vaccination may induce superior humoral immunity compared to homologous vaccination when the priming vaccine is less immunogenic than the boost. However, priming with the more immunogenic vaccine may limit the effect of the heterologous boost.

Notably, the COVID-19 vaccines examined here are monovalent mRNA, adenovirus vectored, or adjuvanted protein-subunit vaccines all targeting the SARS-CoV-2 spike protein, while the leading dengue vaccines are tetravalent, live-attenuated with different parent strains, T cell targets, and humoral responses. These differences limit any direct comparisons regarding the potential benefits and limitations of heterologous COVID-19 versus dengue vaccination. Instead, we can observe the general trends of the COVID 'mix and match' trials and other sequential heterologous and multivalent vaccine studies and hypothesize how these studies might inform future heterologous dengue vaccine trials.

3. Other heterologous and multivalent vaccine studies

Other heterologous vaccine studies have generally focused on prime with viral vector vaccines and boost with subunit vaccines, with the goal of optimizing both cellular and humoral immune responses. These strategies have typically been applied to pathogens that evade immunity such as HIV and HCV [11]. In HIV, vaccine candidates have often been polyvalent, with the goal of broadening the number of antigens recognized by the immune system. For instance, the first HIV vaccine regimen to show any efficacy in humans (30% vaccine efficacy) consisted of a recombinant canarypox vector prime expressing three HIV proteins and a bivalent recombinant envelope protein boost [25]. This has inspired numerous heterologous vaccine trials, including a successful phase 1/2 trial with the aforementioned vaccine adapted for South African HIV strains [26], a subsequent phase 2b/3 trial (NCT02968849) where a heterologous adenoviral vector prime was followed by a adjuvanted subunit boost in Sub-Saharan Africa (NCT03060629), and a study where heterologous vaccination with poxvirus vector vaccine and subunit protein vaccine was trialed both sequentially and simultaneously [27]. The HIV vaccine trials have highlighted the benefits of multivalent heterologous vaccination including improving cellular and humoral responses, broaden-

ing the number of antigens recognized, and bolstering vaccine efficacy [11].

Moreover, HIV trials have indicated that the sequence of heterologous prime boost vaccine is central to immunogenicity. In a human trial of heterologous polyvalent adenovirus (rAd5) and poxvirus (NYVAC-B) vectored HIV vaccines containing HIV proteins from different clades, the rAd5 followed by NYVAC-B boost induced higher cellular and humoral responses than the reverse order [28]. A subsequent mouse study compared heterologous vs. homologous vaccination with a chimeric vesicular stomatitis virus containing the glycoprotein of the lymphocytic choriomeningitis virus (VSV-GP) and a poxvirus (NYVAC), both expressing the same HIV envelope protein. This work also showed that administering the poxvirus-based vaccine second (VSV-GP/NYVAC) induced higher cellular and humoral responses than the reverse heterologous or homologous vaccination [29]. Although the determinants of the superior immunogenicity when the second dose is a poxvirus-vectored HIV vaccine remain unclear, these studies highlight the importance of trialing various vaccine sequences.

Unlike multivalent viral vector or protein subunit HIV vaccines, the leading dengue vaccines are multivalent and live attenuated. The benefits of multivalent live attenuated vaccines (LAV) are widely accepted and evidenced by the success of the oral polio and measles, mumps, and rubella vaccines in eliminating or markedly reducing the morbidity and mortality of these viruses worldwide. Because live attenuated viruses replicate, they can induce durable T and B cell responses against viral antigens in their native conformations [30]. Despite these advantages, no large heterologous vaccination trials have been performed with multivalent LAV to date. The potential of LAV to mimic natural infection is especially compelling in dengue where sequential heterotypic disease is associated with broad immunity.

4. Can sequential heterologous dengue vaccination induce cross-serotypic immunity?

Observations of natural dengue infection have indicated that exposure to two different dengue serotypes induces broad protection even against previously unexposed strains. Specifically, while second heterotypic infection has the highest risk of severe dengue, third and fourth infections are less likely to be symptomatic or serious [31,32]. Immunologic studies have demonstrated that primary dengue infection results in significant protection against the infecting serotype by inducing type-specific antibodies with some cross-serotypic immunity [33]. When the cross-reactive antibodies are at a specific low-titer range, they are strongly associated with severe dengue [34]. This phenomenon is hypothesized to be caused by antibody-dependent enhancement (ADE), where the weak, low-titer antibodies promote viral internalization rather than neutralization, facilitating viral entry and replication in cells with Fc receptors (FcR), and resulting in earlier and higher peak viremia [35]. Enhanced replication can lead to increased virulence and severe disease but also induces potent antibodies that target conserved epitopes and neutralize all four serotypes [36] (Fig. 1).

Induction of this broad immunity has been demonstrated in a small vaccine trial mimicking heterotypic infection by Durbin *et al.* Sequential immunization with monovalent dengue LAV

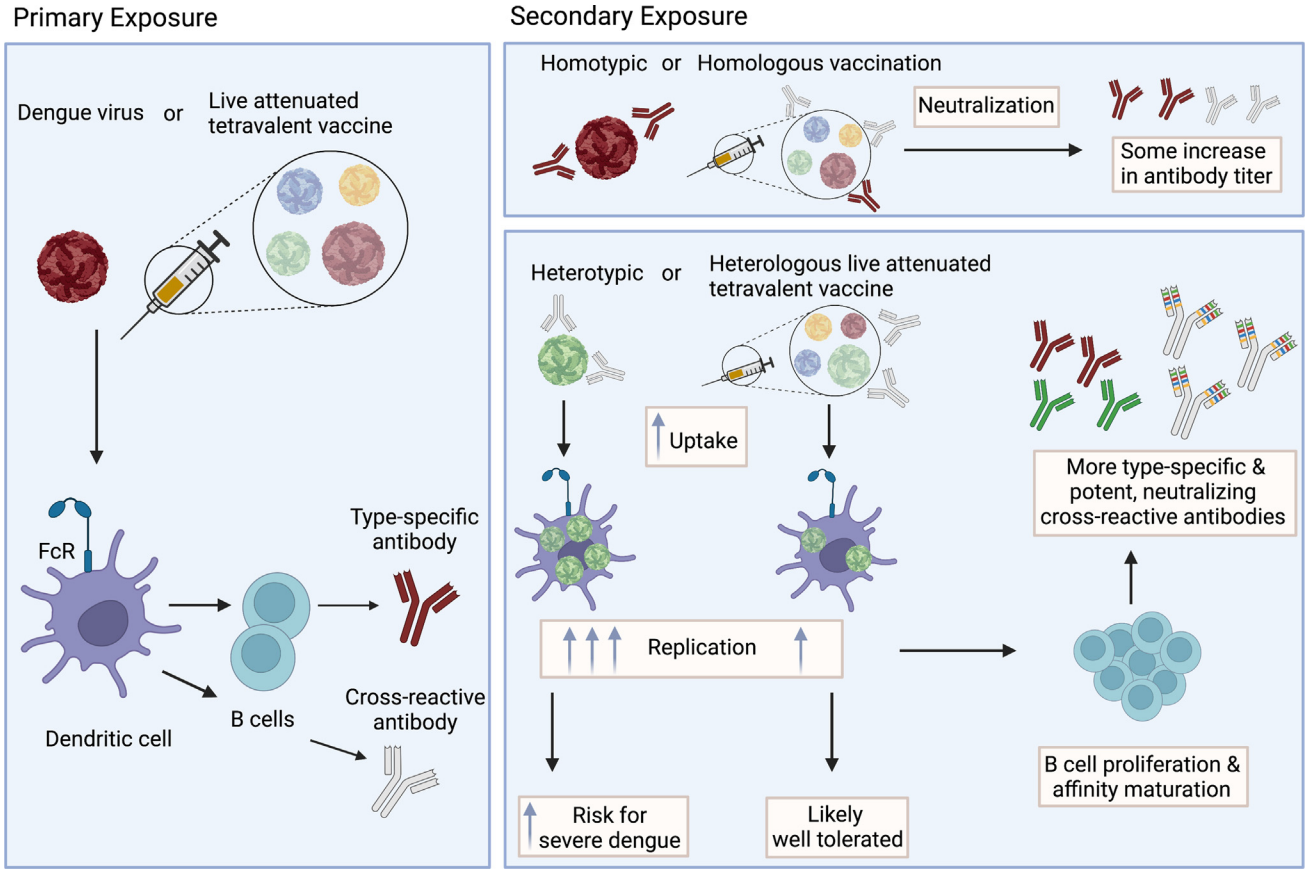

Fig. 1. Sequential heterotypic dengue infection and potential benefits of heterologous dengue vaccination. Primary natural infection and vaccination induce type-specific and cross-reactive antibodies. These antibodies provide strong protection against homologous reinfection but may blunt the immunogenicity of a booster with the same vaccine. Cross-reactive antibodies increase the replication of the second infecting virus, leading to more severe disease but also inducing a robust, broadly neutralizing antibody response. Heterologous vaccination may provide a safe, controlled way to induce broadly neutralizing anti-dengue antibodies.

resulted in earlier onset and higher mean peak viremia after secondary heterotypic versus primary vaccination in one of the four cohorts with no increased adverse effects [37]. Primary immunization induced potent type-specific and weak cross-reactive antibodies, while secondary vaccination resulted in cross-reactive antibodies with high avidity to and strong neutralization of both exposed and nonexposed serotypes [38]. Studies of natural dengue infections have confirmed that type-specific antibodies correlate with protection against dengue disease [33], and cross-reactive antibodies targeting conserved E dimer epitopes (EDE) can potently neutralize all four serotypes [39]. Together, these studies suggest that sequential heterotypic LAV may induce broadly protective antibodies perhaps through the weak cross-reactive antibodies induced by the first exposure enhancing the second exposure. The enhanced second vaccination may have increased immunogenicity due to more antigen production and/or the rapid expansion and affinity maturation of dengue responsive B cells after exposure to conserved and novel epitopes.

4.1. Monovalent vs. tetravalent dengue vaccination

The dengue field has focused on tetravalent vaccination with the aim of avoiding secondary heterotypic natural dengue infection and severe dengue in the period between vaccinations. Further, there is concern that a sequential heterologous vaccination with only two serotypes would not induce tetravalent immunity in all subjects. However, one pre-clinical study suggests that sequential heterotypic monovalent dengue vaccination might be more likely than homologous tetravalent vaccination to induce potent, cross-serotypic dengue antibodies. This study of dengue DNA vaccines in mice reported that compared to homologous tetravalent vaccination, sequential heterotypic monovalent vaccination induced stronger cellular and humoral responses to both exposed and unexposed serotypes [40]. The authors posit that heterologous sequential monovalent immunization may favor the induction of potent broadly neutralizing antibodies by focusing the B cell maturation on conserved residues. In contrast, the simultaneous introduction of multiple variant antigens may limit B cell selection as was observed in an *in silico* model of affinity maturation against HIV [41]. However, an equivalent study has not been performed in human trials.

Interestingly, the two leading dengue vaccines, TAK-003 and Dengvaxia, have some qualities that liken them to DENV2 and DENV4 monovalent vaccines, respectively. Specifically, clinical trial data indicates that the vast majority of viral replication post vaccination consisted of the DENV2 component for TAK-003 and the DENV4 component for Dengvaxia [42,43]. Consistently, antibody depletion assays, which remove cross-neutralizing antibodies to identify type-specific antibodies, have revealed that TAK-003 recipients develop type-specific antibodies primarily against DENV2 while Dengvaxia recipients develop these against DENV4. These antibody responses correlate strongly with the serotype-specific efficacy of each vaccine [44,45]. Additionally, the two vaccines have different parent strains and backbones. TAK-003 is an attenuated DENV2 backbone with chimerized pre-membrane (prM) and envelope (E) proteins from the other serotypes while Dengvaxia consists of a 17D yellow fever vaccine virus backbone chimerized with prM and E proteins from DENV1-4. Thus, these two vaccines may be less likely to neutralize each other and may mimic natural heterotypic infection with DENV2 and DENV4, thereby inducing broadly neutralizing antibodies.

4.2. Other 'mix and match' dengue vaccine trials

Although sequential heterologous trials with tetravalent LAV have never been performed, a number of heterologous dengue vaccination trials have been reported in animals and some in humans [46]. In the early 2000s, multiple animal trials were performed with dengue DNA vaccines with mixed results. In mice and monkeys, a DNA vaccine encoding DENV2 prM and E followed by protein vaccination with DENV2 E2 protein domain III (DIII) did not induce neutralizing antibodies, while simultaneous vaccination with these two products did induce them. However, the antibodies afforded no protection against infectious dengue in a monkey model [47,48]. A separate DNA vaccine encoding both DENV2 E protein DII and III and NS1 followed by a recombinant DENV2 E and NS1 protein vaccine induced low to moderate neutralizing antibodies in mice, and this combination has not been further studied to date [49,50]. In monkeys, heterologous vaccination with either DNA/inactivated virus or DNA/viral replicon particle (VRP) induced neutralizing antibodies, but only the DNA/VRP sequence afforded protection against challenge [48,51]. Additionally, one group examined multiple combinations of DNA and viral vector vaccines, all expressing the DENV2 E protein. In this mouse study, priming with the vaccinia vector vaccine induced the most potent IgG and $CD8^+$ T cell responses while priming with the adenovirus vector vaccine induced stronger $CD4^+$ T cell responses. After viral vector vaccine prime, boost with the DNA vaccine resulted in a stronger stimulation of T cell responses than boost with a different viral vector [52]. These studies suggest that heterologous dengue vaccination does induce different patterns of cellular and humoral immunity, consistent with vaccines against other pathogens. However, because different combinations of DNA vaccines with protein, inactivated virus, or vector vaccines did not consistently induce neutralizing and protective antibodies, the dengue field shifted to LAV.

Of the three leading LAV, TV003 induced the most balanced tetravalent response in phase 1 and 2 trials and homologous boosting did not induce viremia or strengthen the immune response [10,53]. This suggests that the immunity induced by the first dose may neutralize the second. To overcome this, heterologous vaccination has been trialed in two studies of TV003 with protein subunit vaccines. In a human trial, 20 subjects who had received TV003 or TV005 in the 2 to 4 years prior, were boosted with a subunit vaccine consisting of recombinant envelope protein from each of the four serotypes (V180) [54]. Of note, TV005 has the same formulation as TV003 except for a 10-fold higher dose of the DENV2 component. Heterologous boost with V180 resulted in no serious adverse systemic events and a $\geq$ 3-fold peak rise in titers for all serotypes, followed by antibody waning. Although this study could not determine whether the longer vaccination interval (2–4 years versus 1 year) contributed to the superior immunogenicity observed after TV003/V180 compared to TV003/TV003, it suggests that heterologous boosting may stimulate immunity more than homologous boosting, although this immunity may be transient.

The reverse sequence of dengue vaccination was studied in a small monkey trial, where one or two doses of a chimeric subunit vaccine made of DIII-capsid fusions from each serotype (DIIIC) were followed by TV005 [55]. Results revealed that DIIIC/TV005 and 2xDIIIC/TV005, all dosed at 2-month intervals, induced the same level of neutralizing antibodies as homologous TV005, but significantly less TV005-associated viremia was observed in the heterologous vaccine group. This suggests that a protein subunit prime can limit the replication of a LAV without negatively impacting its immunogenicity, potentially representing a strategy to decrease the reactogenicity of LAV.

Apart from TV003, a tetravalent LAV (TLAV) candidate has been studied as part of a heterologous regimen with a tetravalent purified inactivated virus (TPIV) by the Walter Reed Army Institute of Research. In monkeys, TPIV followed by TLAV resulted in high neutralizing titers and protection after challenge [56]. A follow-up phase 1 clinical trial revealed that TPIV/TLAV, at a six-month inter-

val, induced higher neutralizing antibody titers and more balanced and durable cellular responses than the sequence at a 1-month interval, the reverse sequence, or homologous vaccination with either vaccine [57]. However, this TPIV/TLAV regimen was associated with 20% of subjects reporting grade 3 systemic adverse events after heterologous boost, compared to 5% of subjects who received either TLAV/TPIV at a 6-month interval or TPIV/TLAV at a 1-month interval. Additionally, 0–5% of subjects reported grade 3 systemic adverse events after TPIV or TLAV prime, indicating that these vaccines alone are somewhat reactogenic. Although the determinants of higher immunogenicity and reactogenicity after TPIV/TLAV are not known, it is notable that this group had the significantly higher rates of viremia after TLAV compared to other groups. This suggests that the antibodies induced by TPIV may have enhanced TLAV replication. In contrast, the antibodies induced by TLAV may neutralize TPIV boost decreasing the immunogenicity of this combination.

Dengvaxia has also been studied in a small heterologous vaccination clinical trial, where flavivirus naïve participants received either no prime, a monovalent dengue or a yellow fever (YF) LAV [58] followed by one dose of Dengvaxia one year later. The subjects were observed for 180 days post Dengvaxia injection, and the heterologous prime-boost group had significantly higher neutralizing titers for the entire study period, with no increased reactogenicity, laboratory abnormalities, or viremia compared to the flavivirus naïve group. Although this study did not compare two doses of Dengvaxia to heterologous prime boost, it does suggest that heterologous vaccination may bolster humoral immunogenicity.

Thus, in heterologous dengue immunization trials, where one dose was with a live attenuated vaccine, all reported equivalent or increased immunogenicity compared to homologous boost, although one study reported increased reactogenicity. The time interval, sequence, formulation, strength, and reactogenicity of the various vaccines were associated with differences in safety and immunogenicity after heterologous immunization. These observations again highlight the need to trial various heterologous regimens to optimize outcomes.

4.3. Dengue vaccines that have completed phase 3 trials

Although many dengue vaccine candidates have been studied over the past 20+ years, at the time of writing, only Dengvaxia is approved for use. Notably, it is licensed specifically for dengue seropositive individuals, as this group experienced lower rates of dengue disease and hospitalization after vaccination [4]. In contrast, compared to those who received placebo, dengue seronegative people immunized with Dengvaxia had higher rates of hospitalization and severe dengue starting 8 months after the third dose [59]. While the reason for this adverse effect is not confirmed, it is notable that Dengvaxia induces lower antibody titers in seronegative versus seropositive individuals, and the titers wane overtime, especially in the first year post the third vaccination [59,60]. Studies of natural infection have demonstrated that low antibody titers are associated with severe dengue, and ADE is a leading hypothesis to explain this phenomenon [34]. Thus, it is highly plausible that the lower titers induced by Dengvaxia in seronegative individuals enhance subsequent natural infection resulting in higher rates of severe dengue.

Dengvaxia only contains DENV structural proteins from prM and E but not the capsid or any of the seven non-structural proteins. Because both structural and non-structural proteins are required to trigger effective T cell responses, investigators have suggested that lack of dengue non-structural proteins may contribute to Dengvaxia's limited immunogenicity [61]. The only study to investigate cellular immunity induced by Dengvaxia reported that one dose induced $CD8^+$ T cell responses to yellow fever virus and dengue serotype-specific $CD4^+$ T cell responses primarily to the vaccine DENV4 strain [62]. Cross-serotypic $CD4^+$ T cell responses were observed in flavivirus naïve individuals who received two doses of Dengvaxia and in those primed with YF vaccine or monovalent dengue LAV vaccine containing the full DENV genome. Moreover, those primed with the monovalent dengue LAV did develop dengue specific $CD8^+$ T cell responses after Dengvaxia injection, and $CD8^+$ T cell immunity is protective against severe dengue [62,63]. Thus, heterologous prime seems to bolster Dengvaxia's cellular immunogenicity, and may mimic the protective effects of natural infection followed by Dengvaxia.

Aside from Dengvaxia, TAK-003 is the only vaccine to have completed phase 3 clinical trials, and this vaccine also induces lower antibody titers in seronegative vs. seropositive recipients [64]. However, TAK-003 has a better efficacy profile in seronegative individuals except against DENV3, where proportionally (although not significantly) more TAK-003 recipients were hospitalized and developed plasma leakage and thrombocytopenia compared to placebo [7]. TAK-003 is currently being reviewed for licensure by the European Medicines Agency with a decision expected by the end of 2022.

4.4. Future dengue 'mix and match' vaccine trials with leading candidates

The pending approval of a second dengue vaccine moves the field closer to the possibility of heterologous immunization with safe and well-studied vaccines, similar to the approach used for COVID-19 vaccines. Sequential heterologous dengue vaccination may mimic natural heterotypic infection and induce broad immunity by capitalizing on the intrinsic imbalances of existing vaccines, with TAK-003 inducing the strongest immunity against DENV2 and Dengvaxia against DENV4.

The more comprehensive immunity induced by TAK-003 has led experts to propose sequential vaccination with TAK-003 prime followed by Dengvaxia boost [65]. This approach mirrors the classic prime-boost strategy to optimize cellular immunity and is consistent with the observation of stronger T cell responses in COVID-19 trials when adenovirus-vectored vaccination was followed by mRNA boost. Previous small trials have observed that prime with yellow fever or monovalent dengue LAV bolster Dengvaxia's cellular immunogenicity, including inducing a $CD8^+$ T cell response [62]. Moreover, studies of TAK-003 recipients indicate that their T cells do have significant reactivity against the non-structural proteins of DENV1, DENV3, and DENV4 that is less than but directly proportional to their DENV2 response [66]. Thus, if heterologous prime increases TAK-003′s immunogenicity, then the cellular immunity against all serotypes may improve. While combining these vaccines may not induce serotype-specific T cells against all four serotypes, heterologous prime boost with the two leading dengue vaccines may overcome some of the limitations of each vaccine alone.

There are several reasons to consider testing the sequence of Dengvaxia followed by TAK-003 as well (Table 1). First, as was observed in the COVID-19, HIV, and dengue trials of heterologous immunization, the ordering of the vaccines and can greatly impact the immunogenicity of the regimen. Since TAK-003 is a more potent vaccine than Dengvaxia, it could neutralize Dengvaxia boost. Alternatively, Dengvaxia prime could bolster TAK-003′s humoral and cellular responses, and if proven safe, this sequence could benefit the hundreds of thousands who have received Dengvaxia, including those who were seronegative prior to vaccination and those with waning immunity. Given Dengvaxia's adverse effects on seronegative individuals, there may be concern for dosing this vaccine first. However, the benefits of bolstering TAK-003′s

Table 1
Hypothesized advantages and concerns of various prime-boost combinations with the leading dengue vaccines, ordered top to bottom from least to most likely to be immunogenic. Note, Dengvaxia is also called CYD-TDV and is abbreviated here as CYD. TAK-003 is abbreviated here as TAK.

Vaccine Sequence	Advantages	Concerns
CYD/CYD/CYD	Decreases hospitalization in dengue immune individuals.	Increased risk of severe dengue in seronegative people. No dengue capsid or non-structural protein antigens.
TAK/TAK	Induces broad protection in dengue immune individuals. Protects against DENV1 and DENV2 in seronegative individuals.	Limited DENV3 protection and unknown DENV4 protection in seronegative people. Induced mainly DENV2 type-specific antibodies. Immunity against non-structural proteins is primarily against DENV2 with proportionally less immunity to those of other serotypes.
TAK/CYD	TAK will induce immunity against DENV non-structural proteins, especially DENV2. Induce type-specific antibodies against DENV2 and DENV4.	TAK may neutralize CYD, but this could potentially be overcome by increasing vaccine interval. May not broaden T cell response compared to TAK/TAK although heterologous prime did bolster CYD $CD8^+$ T cell responses.
CYD/TAK	Induce type-specific antibodies against DENV2 and DENV4. CYD will not neutralize but may enhance TAK, improving immunogenicity. If safe, could be beneficial for those who have received CYD.	Possible effects of original antigenic sin with giving CYD first, although CYD seems to induce cellular response mostly against yellow fever. Yellow fever immunity is associated with increased response to dengue vaccines.
TV003/TV003	Balanced DENV1-4 immunity in phase 1/2 trials in both seronegative and seropositive individuals.	Phase 3 data not available yet. Does not contain DENV2 non-structural proteins. Second vaccine seems to be neutralized by the first and does not bolster immunity.
TV003/CYD	Different parent strains and backbones may broaden immunity some.	TV003 could neutralize CYD.
CYD/TV003	CYD may enhance TV003 and prime immune cells, improving immunogenicity. If safe, could be beneficial for those who have received CYD.	Could cause more reactogenicity, although this was not seen in trials of flavivirus immune individuals receiving TV003 vaccine.
TV003/TAK	TAK has DENV2 non-structural proteins, which complements TV003 DENV1,3,4 non-structural proteins. Different parent strains.	TV003 could neutralize TAK, although may be less likely than TV003/TV003 given different non-structural proteins and parent strains.
TAK/TV003	May be ideal combination because the vaccine with narrower immune responses is first, complementary T cell antigens.	TAK may enhance TV003 vaccine and increase reactogenicity, although this was not observed in individuals with previous flavivirus exposure who received TV003.

immunogenicity with a Dengvaxia prime may outweigh risks if the vaccination interval is within a half year, well before the increased dengue severity was observed in the clinical trials.

Aside from the ordering, the interval between the vaccines is an important factor in optimizing immunity and safety. Dengue vaccine clinical trials indicated that longer intervals were associated with higher antibody titers. Specifically, 6-month spacing resulted in higher titers than 3-month spacing in the Dengvaxia phase 1 trial [3], and 12-month spacing resulted in higher titers than 3-month spacing in the TAK-003 trial. Takeda did not study a 6-month booster, but they did note that antibody titers primarily waned in the first 6 months [5]. The combination of higher titers with 6- and 12-month boosters and waning antibody levels by 6 months suggests that a 6-month interval may provide optimal immunity.

The potential benefits of 'mix and match' vaccination with Dengvaxia and TAK-003 will need to be weighed against the complexities of clinical practice, especially for dengue naïve individuals. Specifically, dengue naïve individuals have a higher risk of hospitalized dengue starting eight months after receiving the third dose of Dengvaxia, and they are not well protected against DENV3 after receiving two doses of TAK-003 [7,59]. Thus, evaluations of 'mix and match' strategies in dengue naïve individuals would ideally occur in non-endemic areas with novel assays to more accurately predict whether vaccine combinations induce broadly neutralizing antibodies and effective T cell responses. If sequential heterologous vaccination with the two leading dengue vaccine candidates is proven safe and immunogenic, then implementing this strategy in endemic areas would also be complex. Particularly, dengue naïve individuals may be at a higher risk of hospitalized dengue if they receive only one vaccination or two homologous vaccines due to poor adherence, incomplete records, or medical error. Thus, successful 'mix and match' vaccination would depend on informed and adherent patients and providers and may benefit from school-located vaccination programs as well as strategies implemented during the COVID-19 pandemic, such as vaccine ambassadors, medical provider vaccine standardization, and medical reminders [67].

Although still in phase 3 clinical trials, the more balanced tetravalent immunity induced by TV003 makes it a compelling candidate for heterologous prime boost vaccination. Since about 1/3 of subjects did not develop a tetravalent response and homologous boost did not increase immunogenicity, heterologous prime boost with another LAV may optimize the already promising immunogenicity of this vaccine. For example, TAK-003 prime followed by TV003 boost may be ideal since TAK-003 is a narrower vaccine, inducing immune responses focused mainly on DENV2, and is less likely to neutralize TV003. Moreover, these vaccines have complementary Tcell antigens since TAK-003 contains non-structural proteins only from DENV2 while TV003 contains all but DENV2. While it is possible that TAK-003 may enhance TV003 and increase reactogenicity, this type of enhancement was not observed after TV003 vaccination in individuals who had received prior monovalent dengue, yellow fever, or Japanese encephalitis virus vaccines [9]. The pending results of the phase 3 clinical trials may confirm (or refute) the limitations of TV003′s immunogenicity and further support the case for heterologous dengue vaccination.

4.5. Correlates of protection

The safety and efficacy of future vaccine trials, including heterologous vaccination studies, should be evaluated by measuring newly identified correlates of protection against dengue. Antibodies induced by Dengvaxia and TAK-003 neutralized all four DENV strains *in vitro*, but the vaccines' efficacies varied by strain and seropositivity alone did not predict protection. Now, novel assays have been developed that use antibody-depletion and maturation state to measure type-specific and potent cross-reactive antibodies [44,45,68]. Further, regardless of antibody type, neutralizing antibody titers – as measured using classical dengue neutralization assays – that exceed a high specified threshold are strongly

associated with vaccine efficacy, and low average post-vaccination titers are associated with increased dengue hospitalization even in baseline seropositive individuals [69,70]. Recent work has also shown that antibody neutralization of mature Zika virions more accurately predicted protection against Zika challenge in non-human primates and mice [71]. Thus, antibody neutralization of mature DENV virions is expected to be a superior correlate of protection and likely measures both type-specific and cross-reactive protective antibodies.

5. Conclusions

In sum, the theoretical benefits of heterologous prime-boost vaccination have been considered for years with some supporting animal models and clinical trials [11]. The severity of the COVID-19 pandemic and the development of multiple SARS-CoV-2 vaccines have expedited vaccine 'mix and match' trials in humans and highlighted the potential benefits of mixing vaccines that vary in structure and immunogenicity. Results of these trials were so compelling that governments rapidly implemented mix and match vaccination strategies at the population level. Dengue could be the next morbid, widespread disease to benefit from heterologous sequential vaccination. The vaccines that have completed phase 3 clinical trials, Dengvaxia and TAK-003, mimic DENV4 and DENV2 primary infections as evidenced by their type-specific antibody profiles and serotype dependent efficacies. Thus, sequential vaccination may replicate the broad immunity induced by heterotypic natural infection, and there are benefits to trialing both sequences of the vaccines. TV003 is currently in phase 3 trials and induces a more balanced tetravalent response. A heterologous vaccine sequence that includes TV003 may further increase its immunogenicity. The superior immunogenicity of heterologous vaccination may be related to exposure to new epitopes stimulating diverse antibody repertoires and prolonged affinity maturation, and for viruses that replicate in cells with FcR, mild enhancement of the second exposure by the first leading to more antigen production. Identification of robust correlates of protection and enhancement will further enable evaluation of the safety and efficacy of these strategies.

Data availability

No data was used for the research described in the article.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] Zeng Z, Zhan J, Chen L, Chen H, Cheng S. Global, regional, and national dengue burden from 1990 to 2017: a systematic analysis based on the global burden of disease study 2017. eClinicalMedicine 2021;32:100712.
[2] Wilder-Smith A. Dengue vaccine development by the year 2020: challenges and prospects. Curr Opin Virol 2020;43:71–8.
[3] Morrison D, Legg TJ, Billings CW, Forrat R, Yoksan S, Lang J. A novel tetravalent dengue vaccine is well tolerated and immunogenic against all 4 serotypes in flavivirus-naive adults. J Infect Dis 2010;201:370–7.
[4] Forrat R, Dayan GH, DiazGranados CA, Bonaparte M, Laot T, Capeding MR, et al. Analysis of hospitalized and severe dengue cases over the 6 years of follow-up of the tetravalent dengue vaccine (CYD-TDV) efficacy trials in Asia and Latin America. Clin Infect Dis 2021;73:1003–12.
[5] Sáez-Llorens X, Tricou V, Yu D, Rivera L, Tuboi S, Garbes P, et al. Safety and immunogenicity of one versus two doses of Takeda's tetravalent dengue vaccine in children in Asia and Latin America: interim results from a phase 2, randomised, placebo-controlled study. Lancet Infect Dis 2017;17:615–25.
[6] Lopez-Medina E, Biswal S, Saez-Llorens X, Borja-Tabora C, Bravo L, Sirivichayakul C, et al. Efficacy of a dengue vaccine candidate (TAK-003) in healthy children and adolescents two years after vaccination. J Infect Dis 2020;225:1521–32.
[7] Rivera L, Biswal S, Sáez-Llorens X, Reynales H, López-Medina E, Borja-Tabora C, et al. Three-year efficacy and safety of Takeda's dengue vaccine candidate (TAK-003). Clin Infect Dis 2022;75:107–17.
[8] Kirkpatrick BD, Durbin AP, Pierce KK, Carmolli MP, Tibery CM, Grier PL, et al. Robust and balanced immune responses to all 4 dengue virus serotypes following administration of a single dose of a live attenuated tetravalent dengue vaccine to healthy Flavivirus-Naive Adults. J Infect Dis 2015;212:702–10.
[9] Whitehead SS, Durbin AP, Pierce KK, Elwood D, McElvany BD, Fraser EA, et al. In a randomized trial, the live attenuated tetravalent dengue vaccine TV003 is well-tolerated and highly immunogenic in subjects with flavivirus exposure prior to vaccination. PLoS Negl Trop Dis 2017;11:e0005584.
[10] Kallas EG, Precioso AR, Palacios R, Thomé B, Braga PE, Vanni T, et al. Safety and immunogenicity of the tetravalent, live-attenuated dengue vaccine Butantan-DV in adults in Brazil: a two-step, double-blind, randomised placebo-controlled phase 2 trial. Lancet Infect Dis 2020;20:839–50.
[11] Kardani K, Bolhassani A, Shahbazi S. Prime-boost vaccine strategy against viral infections: mechanisms and benefits. Vaccine 2016;34:413–23.
[12] Andrews SF, Chambers MJ, Schramm CA, Plyler J, Raab JE, Kanekiyo M, et al. Activation Dynamics and immunoglobulin evolution of pre-existing and newly generated human memory B cell responses to influenza hemagglutinin. Immunity 2019;51:398–410.e5.
[13] Greinacher A, Thiele T, Warkentin TE, Weisser K, Kyrle PA, Eichinger S. Thrombotic thrombocytopenia after ChAdOx1 nCov-19 Vaccination. N Engl J Med 2021;384:2092–101.
[14] Overview of EU/EEA country recommendations on COVID-19 vaccination with Vaxzevria, and a scoping review of evidence to guide decision-making. Stockholm: European Centre for Disease Prevention and Control; 2021.
[15] Dimeglio C, Herin F, Da-Silva I, Jougla I, Pradere C, Porcheron M, et al. Heterologous ChAdOx1-S/BNT162b2 vaccination: neutralizing antibody response to SARS-CoV-2. Clin Infect Dis 2022;74:1315–6.
[16] Schmidt T, Klemis V, Schub D, Mihm J, Hielscher F, Marx S, et al. Immunogenicity and reactogenicity of heterologous ChAdOx1 nCoV-19/mRNA vaccination. Nat Med 2021;27:1530–5.
[17] Tenbusch M, Schumacher S, Vogel E, Priller A, Held J, Steininger P, et al. Heterologous prime-boost vaccination with ChAdOx1 nCoV-19 and BNT162b2. Lancet Infect Dis 2021;21:1212–3.
[18] Pozzetto B, Legros V, Djebali S, Barateau V, Guibert N, Villard M, et al. Immunogenicity and efficacy of heterologous ChadOx1/BNT162b2 vaccination. Nature 2021;600:701–6.
[19] Hillus D, Schwarz T, Tober-Lau P, Vanshylla K, Hastor H, Thibeault C, et al. Safety, reactogenicity, and immunogenicity of homologous and heterologous prime-boost immunisation with ChAdOx1 nCoV-19 and BNT162b2: a prospective cohort study. Lancet Respir Med 2021;9:1255–65.
[20] Nordström P, Ballin M, Nordström A. Effectiveness of heterologous ChAdOx1 nCoV-19 and mRNA prime-boost vaccination against symptomatic Covid-19 infection in Sweden: A nationwide cohort study. Lancet Reg Health Eur 2021;11:100249.
[21] Liu X, Shaw RH, Stuart ASV, Greenland M, Aley PK, Andrews NJ, et al. Safety and immunogenicity of heterologous versus homologous prime-boost schedules with an adenoviral vectored and mRNA COVID-19 vaccine (Com-COV): a single-blind, randomised, non-inferiority trial. Lancet 2021;398:856–69.
[22] Stuart ASV, Shaw RH, Liu X, Greenland M, Aley PK, Andrews NJ, et al. Immunogenicity, safety, and reactogenicity of heterologous COVID-19 primary vaccination incorporating mRNA, viral-vector, and protein-adjuvant vaccines in the UK (Com-COV2): a single-blind, randomised, phase 2, non-inferiority trial. Lancet 2022;399:36–49.
[23] Munro APS, Janani L, Cornelius V, Aley PK, Babbage G, Baxter D, et al. Safety and immunogenicity of seven COVID-19 vaccines as a third dose (booster) following two doses of ChAdOx1 nCov-19 or BNT162b2 in the UK (COV-BOOST): a blinded, multicentre, randomised, controlled, phase 2 trial. Lancet 2021;398:2258–76.
[24] Atmar RL, Lyke KE, Deming ME, Jackson LA, Branche AR, El Sahly HM, et al. Homologous and heterologous Covid-19 booster vaccinations. N Engl J Med 2022;386:1046–57.
[25] Rerks-Ngarm S, Pitisuttithum P, Nitayaphan S, Kaewkungwal J, Chiu J, Paris R, et al. Vaccination with ALVAC and AIDSVAX to Prevent HIV-1 Infection in Thailand. N Engl J Med 2009;361:2209–20.
[26] Bekker L-G, Moodie Z, Grunenberg N, Laher F, Tomaras GD, Cohen KW, et al. Subtype C ALVAC-HIV and bivalent subtype C gp120/MF59 HIV-1 vaccine in low-risk, HIV-uninfected, South African adults: a phase 1/2 trial. The Lancet HIV 2018;5:e366–78.
[27] Pantaleo G, Janes H, Karuna S, Grant S, Ouedraogo GL, Allen M, et al. Safety and immunogenicity of a multivalent HIV vaccine comprising envelope protein with either DNA or NYVAC vectors (HVTN 096): a phase 1b, double-blind, placebo-controlled trial. The Lancet HIV 2019;6:e737–49.

[28] Bart P-A, Huang Y, Karuna ST, Chappuis S, Gaillard J, Kochar N, et al. HIV-specific humoral responses benefit from stronger prime in phase Ib clinical trial. J Clin Investig 2014;124:4843–56.
[29] Perdiguero B, Gómez CE, García-Arriaza J, Sánchez-Corzo C, Sorzano CÓS, Wilmschen S, et al. Heterologous Combination of VSV-GP and NYVAC Vectors Expressing HIV-1 Trimeric gp145 Env as Vaccination Strategy to Induce Balanced B and T Cell Immune Responses. Front Immunol 2019;10:2941.
[30] Pollard AJ, Bijker EM. A guide to vaccinology: from basic principles to new developments. Nat Rev Immunol 2021;21:83–100.
[31] Gibbons RV, Kalanarooj S, Jarman RG, Nisalak A, Vaughn DW, Endy TP, et al. Analysis of repeat hospital admissions for dengue to estimate the frequency of third or fourth dengue infections resulting in admissions and dengue hemorrhagic fever, and serotype sequences. Am J Trop Med Hyg 2007;77:910–3.
[32] Olkowski S, Forshey BM, Morrison AC, Rocha C, Vilcarromero S, Halsey ES, et al. Reduced risk of disease during postsecondary dengue virus infections. J Infect Dis 2013;208:1026–33.
[33] Henein S, Adams C, Bonaparte M, Moser JM, Munteanu A, Baric R, et al. Dengue vaccine breakthrough infections reveal properties of neutralizing antibodies linked to protection. J Clin Invest 2021;131:e147066.
[34] Katzelnick LC, Gresh L, Halloran ME, Mercado JC, Kuan G, Gordon A, et al. Antibody-dependent enhancement of severe dengue disease in humans. Science 2017;358:929–32.
[35] Halstead SB. In vivo enhancement of dengue virus infection in rhesus monkeys by passively transferred antibody. J Infect Dis 1979;140:527–33.
[36] Rouvinski A, Guardado-Calvo P, Barba-Spaeth G, Duquerroy S, Vaney M-C, Kikuti CM, et al. Recognition determinants of broadly neutralizing human antibodies against dengue viruses. Nature 2015;520:109–13.
[37] Durbin AP, Schmidt A, Elwood D, Wanionek KA, Lovchik J, Thumar B, et al. Heterotypic dengue infection with live attenuated monotypic dengue virus vaccines: implications for vaccination of populations in areas where dengue is endemic. J Infect Dis 2011;203:327–34.
[38] Tsai WY, Durbin A, Tsai JJ, Hsieh SC, Whitehead S, Wang WK. Complexity of neutralizing antibodies against multiple dengue virus serotypes after heterotypic immunization and secondary infection revealed by in-depth analysis of cross-reactive antibodies. J Virol 2015;89:7348–62.
[39] Durham ND, Agrawal A, Waltari E, Croote D, Zanini F, Fouch M, et al. Broadly neutralizing human antibodies against dengue virus identified by single B cell transcriptomics. Elife 2019;8:e52384.
[40] Hou J, Shrivastava S, Loo HL, Wong LH, Ooi EE, Chen J. Sequential immunization induces strong and broad immunity against all four dengue virus serotypes. NPJ Vaccines 2020;5:68.
[41] Wang S, Mata-Fink J, Kriegsman B, Hanson M, Irvine Darrell J, Eisen Herman N, et al. Manipulating the selection forces during affinity maturation to generate cross-reactive HIV antibodies. Cell 2015;160:785–97.
[42] Rupp R, Luckasen GJ, Kirstein JL, Osorio JE, Santangelo JD, Raanan M, et al. Safety and immunogenicity of different doses and schedules of a live attenuated tetravalent dengue vaccine (TDV) in healthy adults: A Phase 1b randomized study. Vaccine 2015;33:6351–9.
[43] Dayan GH, Thakur M, Boaz M, Johnson C. Safety and immunogenicity of three tetravalent dengue vaccine formulations in healthy adults in the USA. Vaccine 2013;31:5047–54.
[44] White LJ, Young EF, Stoops MJ, Henein SR, Adams EC, Baric RS, et al. Defining levels of dengue virus serotype-specific neutralizing antibodies induced by a live attenuated tetravalent dengue vaccine (TAK-003). PLoS Negl Trop Dis 2021;15:e0009258.
[45] Henein S, Swanstrom J, Byers AM, Moser JM, Shaik SF, Bonaparte M, et al. Dissecting antibodies induced by a chimeric yellow fever-dengue, live-attenuated, tetravalent dengue vaccine (CYD-TDV) in naive and dengue-exposed individuals. J Infect Dis 2017;215:351–8.
[46] Valdés I, Lazo L, Hermida L, Guillén G, Gil L. Can complementary prime-boost immunization strategies be an alternative and promising vaccine approach against dengue virus? Front Immunol 2019;10:1956.
[47] Simmons M, Murphy GS, Kochel T, Raviprakash K, Hayes CG. Characterization of antibody responses to combinations of a dengue-2 DNA and dengue-2 recombinant subunit vaccine. Am J Trop Med Hyg 2001;65:420–6.
[48] Simmons M, Porter KR, Hayes CG, Vaughn DW, Putnak R. Characterization of antibody responses to combinations of a dengue virus type 2 DNA vaccine and two dengue virus type 2 protein vaccines in rhesus macaques. J Virol 2006;80:9577–85.
[49] Mellado-Sánchez G, García-Cordero J, Luria-Pérez R, Lázaro-Olan L, Santos-Argumedo L, Gutiérrez-Castañeda B, et al. DNA priming E and NS1 constructs–homologous proteins boosting immunization strategy to improve immune response against dengue in mice. Viral Immunol 2005;18:709–21.
[50] Mellado-Sánchez G, García-Machorro J, Sandoval-Montes C, Gutiérrez-Castañeda B, Rojo-Domínguez A, García-Cordero J, et al. A plasmid encoding parts of the dengue virus E and NS1 proteins induces an immune response in a mouse model. Arch Virol. 2010;155:847-56.
[51] Chen L, Ewing D, Subramanian H, Block K, Rayner J, Alterson KD, et al. A heterologous DNA prime-Venezuelan equine encephalitis virus replicon particle boost dengue vaccine regimen affords complete protection from virus challenge in cynomolgus macaques. J Virol 2007;81:11634–9.
[52] George JA, Eo SK. Distinct humoral and cellular immunity induced by alternating prime-boost vaccination using plasmid DNA and live viral vector vaccines expressing the E protein of dengue virus type 2. Immune Netw 2011;11:268–80.
[53] Durbin AP, Kirkpatrick BD, Pierce KK, Carmolli MP, Tibery CM, Grier PL, et al. A 12-month-interval dosing study in adults indicates that a single dose of the National Institute of Allergy and Infectious Diseases tetravalent dengue vaccine induces a robust neutralizing antibody response. J Infect Dis 2016;214:832–5.
[54] Durbin AP, Pierce KK, Kirkpatrick BD, Grier P, Sabundayo BP, He H, et al. Immunogenicity and safety of a tetravalent recombinant subunit dengue vaccine in adults previously vaccinated with a live attenuated tetravalent dengue vaccine: results of a phase-i randomized clinical trial. Am J Trop Med Hyg 2020;103:855–63.
[55] Valdés I, Izquierdo A, Cobas K, Thao P, Anh Duc H, Duc Loc H, et al. A heterologous prime-boost strategy for immunization against Dengue virus combining the Tetra DIIIC subunit vaccine candidate with the TV005 live-attenuated tetravalent vaccine. J Gen Virol 2019;100:975–84.
[56] Simmons M, Burgess T, Lynch J, Putnak R. Protection against dengue virus by non-replicating and live attenuated vaccines used together in a prime boost vaccination strategy. Virology 2010;396:280–8.
[57] Lin L, Koren MA, Paolino KM, Eckels KH, De La Barrera R, Friberg H, et al. Immunogenicity of a live-attenuated dengue vaccine using a heterologous prime-boost strategy in a phase 1 randomized clinical trial. J Infect Dis 2021;223:1707–16.
[58] Qiao M, Shaw D, Forrat R, Wartel-Tram A, Lang J. Priming effect of dengue and yellow fever vaccination on the immunogenicity, infectivity, and safety of a tetravalent dengue vaccine in humans. Am J Trop Med Hyg 2011;85:724–31.
[59] Sridhar S, Luedtke A, Langevin E, Zhu M, Bonaparte M, Machabert T, et al. Effect of dengue serostatus on dengue vaccine safety and efficacy. N Engl J Med 2018;379:327–40.
[60] Capeding MR, Laot TM, Boaz M, Wartel TA, Crevat D. Immunogenicity and safety of a tetravalent dengue vaccine during a five-year follow-up period. Trials in Vaccinology 2015;4:19–23.
[61] Tian Y, Grifoni A, Sette A, Weiskopf D. Human T cell response to dengue virus infection. Front Immunol 2019;10:2125.
[62] Guy B, Nougarede N, Begue S, Sanchez V, Souag N, Carre M, et al. Cell-mediated immunity induced by chimeric tetravalent dengue vaccine in naive or flavivirus-primed subjects. Vaccine 2008;26:5712–21.
[63] Weiskopf D, Angelo MA, de Azeredo EL, Sidney J, Greenbaum JA, Fernando AN, et al. Comprehensive analysis of dengue virus-specific responses supports an HLA-linked protective role for CD8+ T cells. Proc Natl Acad Sci USA 2013;110:E2046–53.
[64] Biswal S, Borja-Tabora C, Martinez Vargas L, Velásquez H, Theresa Alera M, Sierra V, et al. Efficacy of a tetravalent dengue vaccine in healthy children aged 4–16 years: a randomised, placebo-controlled, phase 3 trial. The Lancet 2020;395:1423–33.
[65] Macias A, Ruiz-Palacios G, Ramos-Castaneda J. Combine dengue vaccines to optimize effectiveness. Vaccine 2020;38:4801–4.
[66] Waickman AT, Friberg H, Gargulak M, Kong A, Polhemus M, Endy T, et al. Assessing the diversity and stability of cellular immunity generated in response to the candidate live-attenuated dengue virus vaccine TAK-003. Front Immunol 2019;10:1778.
[67] Centers for Disease Control and Prevention.. 12 COVID-19 Vaccination Strategies for Your Community. Vaccines & Immunizations 2021. https://www.cdc.gov/vaccines/covid-19/vaccinate-with-confidence/community.html.
[68] Raut R, Corbett KS, Tennekoon RN, Premawansa S, Wijewickrama A, Premawansa G, et al. Dengue type 1 viruses circulating in humans are highly infectious and poorly neutralized by human antibodies. Proc Natl Acad Sci USA 2019;116:227–32.
[69] Huang Y, Williamson BD, Moodie Z, Carpp LN, Chambonneau L, DiazGranados CA, et al. Analysis of neutralizing antibodies as a correlate of instantaneous risk of hospitalized dengue in placebo recipients of dengue vaccine efficacy trials. J Infect Dis 2022;225:332–40.
[70] Moodie Z, Juraska M, Huang Y, Zhuang Y, Fong Y, Carpp LN, et al. Neutralizing antibody correlates analysis of tetravalent dengue vaccine efficacy trials in Asia and Latin America. J Infect Dis 2018;217:742–53.
[71] Maciejewski S, Ruckwardt TJ, Morabito KM, Foreman BM, Burgomaster KE, Gordon DN, et al. Distinct neutralizing antibody correlates of protection among related Zika virus vaccines identify a role for antibody quality. Sci Transl Med 2020;12:eaaw9066.