Anhang zur wissenschaftlichen Begründung der Ständigen Impfkommission (STIKO) zur Dengue-Impfempfehlung mit dem Impfstoff Qdenga

Inhaltsverzeichnis

1. Beschreibung und Ausschlusskriterien bereits publizierter systematischer Reviews zur Wirksamkeit und Sicherheit von Qdenga

Vor Durchführung der systematischen Literaturrecherche zur Sicherheit und Wirksamkeit von Qdenga wurde im Sysvac-Register und Prospero nach bereits existierenden systematischen Reviews gesucht und deren Verwendbarkeit geprüft. Zwei systematische Reviews wurden derart identifiziert, die im Folgenden dargestellt sind.

Foucambert et al., 2022 „Efficacy of Dengue Vaccines in the Prevention of Severe Dengue in Children: A Systematic Review"

Der systematische Review von Foucambert et al. (1) untersucht die Vakzineeffektivität (VE) von Dengue-Impfstoffen zur Verhinderung von schwerem Dengue bei Kindern. Von der im April 2022 in verschiedenen Datenbanken durchgeführten Literatursuche wurden 11 Studien in den Review eingeschlossen. Zwei der elf Studien beurteilten die VE von Qdenga (TAK-003) (Biswal et al., 2020 (2) und Tricou et al., 2020 (3)). Detaillierte Effektivitätsdaten, stratifiziert nach Serotyp, Serostatus vor Impfung und Alter sind im Review nicht genannt. Die AutorInnen des Reviews kommen zu der Conclusio, dass TAK-003 effektiv Fälle schweren Dengues und Dengue Hämorrhagisches Fieber (DHF) verhindern kann und effektiv in allen betrachteten Altersgruppen sowohl bei seronegativen und seropositiven Kindern ist.

Die STIKO-Geschäftsstelle beurteilte den Review anhand von Amstar 2 (4) und schätzt die Qualität des Review als gering ein, u. a. aufgrund eines nicht vorab publizierten Studienprotokolls, einer nicht näher definierten und nicht extrahierten Vergleichsgruppe und fehlender Erläuterung zu den eingeschlossenen bzw. ausgeschlossenen Studien und den Förderungsdetails der Studien.

Kautsar et al., 2023 „Systematic Review and Meta-Analysis of Randomized Trials: Efficacy, Immunogenicity, and Safety of DenvaxVaccine"

Der Review von Kautsar et al. ist derzeit nur als Konferenzposter erhältlich und nicht final publiziert. Daher kann die Methodik nicht abschließend beurteilt werden und die Ergebnisse nicht verwendet werden.

Anhand der verfügbaren Daten lässt sich die methodische Qualität der identifizierten Übersichtsarbeit zwar nicht abschließend beurteilen, die publizierten Daten weisen aber folgende methodische Mängel auf: Der Review inkludiert 9 Studien zu TAK-003, wobei 2 bzw. 3 aus jeweils einer Studie hervorgehen. In die Metaanalyse zur VE, die über alle Seroptypen hinweg sowie für die Serotypen DENV1-4 stratifiziert durchgeführt wurde, sind Daten aus Biswal et al., 2019 (5), Biswal et al., 2020 (2) und Lopéz-Medina et al., 2022 (6) eingeschlossen, die Fälle an VCD zu unterschiedlichen Zeitpunkten der TIDES-Studie berichten (Biswal et al., 2019 (5): 12 Monate nach 2. Impfstoffdosis, Biswal et al., 2020 (2): 17 Monate nach 2. Impfstoffdosis, Lopéz-Medina et al., 2022 (6): 24 Monate nach 2. Impfstoffdosis bei Personen, die bei Studienbeginn seropositiv waren). Es kann somit nicht ausgeschlossen werden, dass hier Fälle und Kontrollen mehrfach gezählt wurden.

Für die Meta-Analyse zur Immunogenität des Impfstoffs wurden zwei Studien (Biswal et al., 2020 (2) und Sirivichayakul et al., 2022 (7)) inkludiert. Trotz schriftlicher Kommunikation mit dem Autorenteam des Reviews konnte nicht eruiert werden, auf welche Immunogenitätsdaten sich der Review bezieht.

Die Metaanalyse zur Sicherheit umfasst auch Dosisfindungsstudien und ist daher nur eingeschränkt zu interpretieren. Die Zuordnung von lokalen oder systemischen Nebenwirkungen zu Studien ist nicht immer nachvollziehbar, z. B. wurden in Lopéz-Medina et al., 2022 keine Lokalreaktionen oder allgemeine Symptome wie Kopfschmerzen oder Myalgien berichtet, werden aber in der Metaanalyse aufgezählt (6).

2. Suchstrategie zur Literaturrecherche zur Wirksamkeit und Sicherheit von QDENGA

Suchstrategie:

Suche in MEDLINE, EMBASE und Referenzlisten von relevanten Publikationen (Datum der Suche: 06.02.2023)

PubMed

#1	"dengue vaccines"[MeSH Terms] OR ("dengue"[Title/Abstract] AND "vaccination"[Title/Abstract] AND 2020/01/01:2023/12/31[Date - Publication]) OR ("dengue"[Title/Abstract] AND "vaccine"[Title/Abstract] AND 2020/01/01:2023/12/31[Date - Publication]) OR ("dengue"[Title/Abstract] AND "vaccinated"[Title/Abstract] AND 2020/01/01:2023/12/31[Date - Publication]) OR ("dengue"[Title/Abstract] AND

	"immunization"[Title/Abstract] AND 2020/01/01:2023/12/31[Date - Publication]) OR ("dengue"[Title/Abstract] AND "immunisation"[Title/Abstract] AND 2020/01/01:2023/12/31[Date - Publication]) OR ("dengue"[Title/Abstract] AND "immunized"[Title/Abstract] AND 2020/01/01:2023/12/31[Date - Publication]) OR ("dengue"[Title/Abstract] AND "immunised"[Title/Abstract] AND 2020/01/01:2023/12/31[Date - Publication]) OR "TAK 003"[All Fields] OR "TAK003"[All Fields] OR ("DENV-2"[Title/Abstract] AND "vaccination"[Title/Abstract]) OR ("DENV-2"[Title/Abstract] AND "vaccine"[Title/Abstract]) OR ("DENV-2"[Title/Abstract] AND "vaccinated"[Title/Abstract]) OR ("DENV2"[Title/Abstract] AND "vaccination"[Title/Abstract]) OR ("tetravalent"[Title/Abstract] AND "dengue"[Title/Abstract] AND "vaccin*"[Title/Abstract]) OR ("dengue"[Title/Abstract] AND "vaccine"[Title/Abstract] AND 2020/01/01:2023/12/31[Date - Publication]) OR ("DENV-2"[Title/Abstract] AND "vaccines"[Title/Abstract]) OR ("DENV2"[Title/Abstract] AND "vaccines"[Title/Abstract]) OR ("DENV2"[Title/Abstract] AND "vaccine"[Title/Abstract]) AND (2016:2023[pdat])

EMBASE

#1	('qdenga' (all fields) OR 'dengue vaccine'/exp OR ('dengue':ti,ab AND 'vaccination':ti,ab AND (2020:py OR 2021:py OR 2022:py OR 2023:py)) OR ('dengue':ti,ab AND 'vaccine':ti,ab AND (2020:py OR 2021:py OR 2022:py OR 2023:py)) OR ('dengue':ti,ab AND 'vaccinated':ti,ab AND (2020:py OR 2021:py OR 2022:py OR 2023:py)) OR ('dengue':ti,ab AND 'immunization':ti,ab AND (2020:py OR 2021:py OR 2022:py OR 2023:py)) OR ('dengue':ti,ab AND 'immunisation':ti,ab AND (2020:py OR 2021:py OR 2022:py OR 2023:py)) OR ('dengue':ti,ab AND 'immunized':ti,ab AND (2020:py OR 2021:py OR 2022:py OR 2023:py)) OR ('dengue':ti,ab AND 'immunised':ti,ab AND (2020:py OR 2021:py OR 2022:py OR 2023:py)) OR ('tak 003' OR 'tak003') OR ('denv2':ti,ab AND ('vaccination':ti,ab OR 'vaccine':ti,ab OR 'vaccines':ti,ab OR 'vaccinated':ti,ab)) OR ('denv-2':ti,ab AND ('vaccination':ti,ab OR 'vaccine':ti,ab OR 'vaccines':ti,ab OR 'vaccinated':ti,ab)) OR ('tetravalent':ti,ab AND 'dengue':ti,ab AND 'vaccin*':ti,ab) OR ('takeda':ti,ab AND 'dengue':ti,ab)) AND (2016:py OR 2017:py OR 2018:py OR 2019:py OR 2020:py OR 2021:py OR 2022:py OR 2023:py)

3. Ein- und Ausschlusskriterien für die Identifikation von relevanten Studien zur Beurteilung der Wirksamkeit und Sicherheit von Qdenga

PICO-Kriterium	Einschluss-Kriterium
Population	Personen jeden Geschlechts und aller Altersgruppen; unabhängig einer früher diagnostizierten Dengue-Infektion; unabhängig davon ob sie sich in Dengue-endemischen oder nicht-endemischen Gebieten aufhalten
Intervention	Impfung mit TAK-003/Qdenga/Takeda tetravalent dengue vaccine, Denvax complete dosing schedules

Comperator	· Keine Impfung · Impfung mit Placebo · Impfung mit anderem Impfstoff, der nicht gegen Dengue gerichtet ist. · Ko-administration · Impfung für die eine mögliche Kreuzprotektion angenommen werden kann (z.B. Gelbfieber-Impfstoff, Impfstoff gegen Japanische Enzephalitis)
Outcome - Wirksamkeit	· Jegliche Immunogenitätsdaten gegen Dengue (Erhebung Impfinduzierter Serotypspezifischer Antikörper (GMT); · Dengue Infektion (virologically confirmed dengue, VCD), bestätigt durch Serotyp-spezifische PCR oder NS1-Ag-test); · Schwere Dengue gemäß der WHO Definition von 2009
Outcome - Sicherheit	· Lokale Reaktionen · Systemische Reaktionen · Schwere unerwünschte Arzneimittelwirkungen (inkl. Tod) · Unerwünschte Ereignisse besonderen Interesses (adverse events of special interest, AESI): schweres Dengue gemäß der WHO-Definition von 2009 in baseline sero-negativen Personen
Study design	· Randomisiert kontrollierte Studien (randomized controlled trials, RCT) · Nicht-RCTs mit Kontrollgruppe · Für Sicherheitsstudien: nur Phase 2/3 Studien, Phase 4 Studien und nicht-randomisierte Studien mit einer Kontrollgruppe
Angewandte Filter: · Sprache · Zeitpunkt der Publikation	 · Englisch, Deutsch Französisch, Spanisch · Publikation seit 01/01/2016

4. Liste der ausgeschlossenen Studien

No	Reference	Exclusion criteria
1	Agarwal R, Wahid MH, Yausep OE, Angel SH, Lokeswara AW. The Immunogenicity and Safety of CYD-Tetravalent Dengue Vaccine (CYD-TDV) in Children and Adolescents: A Systematic Review; Acta Med Indones 2017;49(1):24-33	wrong intervention
2	Aguiar M, Stollenwerk N. The impact of serotype cross-protection on vaccine trials: Denvax as a case study; Vaccines 2020; 8(4): 1-12 doi: 10.3390/vaccines8040674	wrong outcome
3	Biswal S. Efficacy of a tetravalent dengue vaccine in healthy 4 to 16 year-old children; 2019; American Journal of Tropical Medicine and Hygiene 2019; 101 (5): 418-419 doi: 10.4269/ajtmh.abstract2019	wrong study design
4	Biswal S, Lefevre I, Tricou V, Rauscher M, Borkowski A. Takeda's tetravalent dengue vaccine-two years efficacy surveillance; American Journal of Tropical Medicine and Hygiene 2020; 103 (S5): 139-40	wrong study design
5	Biswal S, Patel SS, Rauscher M. Safety of Dengue Vaccine? Clin Infect Dis 2022 doi: 10.1093/cid/ciac808	insufficient data for extraction
6	Biswal S, Tricou V, Dean H. Tetravalent Dengue Vaccine in Healthy Children. Reply; N Engl J Med 2020; 382 (18): 1770-1771 doi: 10.1056/NEJMc2000987	wrong study design
7	Braun R.S., Sharma M, DeMaso C, Parker A, Dominguez D, Watkins H, Dean H, Karwal L, Nascimento E,.Messere N, Tsuji I, Zahralban-Steele M, Currier JR, Friberg-Robertson H. Characterization of Immune Responses to a Live-Attenuated Tetravalent Dengue Vaccine; Open Forum Infectious Diseases 2021; 8 (S1):S615 doi: 10.1093/ofid/ofab466.1245	wrong outcome
8	Currier J.R., Friberg H, Tricou H, Egan V, Victor M, Hatch K, Low K, Oh J, Jarman H, Wallace R, Dean H. Cell-mediated immunity generated by Takeda's live attenuated dengue vaccine (TDV); Journal of Tropical Medicine and Hygiene 2018; 99(4):241	wrong outcome
9	DeMaso CR, Karwal L, Zahralban-Steele M, Dominguez D, Springer ZL, Kaiser M, Palani S, Rindfleisch T, Bohning K, Hather G, Das S, Sharma M, Dean HJ. Specificity and Breadth of the Neutralizing Antibody Response to a Live-Attenuated Tetravalent Dengue Vaccine; J Infect Dis 2022; 226(11):1959-1963 doi: 10.1093/infdis/jiac272	wrong study design
10	de Silva A, White L. Immunogenicity of a Live Dengue Vaccine (TAK-003); J Infect Dis 2022, 227(1):163-164 doi: 10.1093/infdis/jiac424	wrong study design
11	Dean HJ, Egan MA, Wallace D. Comprehensive analysis of the immune response elicited by Takeda's tetravalent dengue vaccine candidate; American Journal of Tropical Medicine and Hygiene 2018; 99(4):242	wrong study design
12	Department of Error: Efficacy of a tetravalent dengue vaccine in healthy children aged 4–16 years: a randomised, placebo-controlled, phase 3 trial (The Lancet, (S0140673620304141), (10.1016/S0140-6736(20)30414-1)); The Lancet 2020; 395(10230): 1114 doi: 10.1016/S0140-6736(20)30682-6	wrong study design
13	Friberg H, Hatch K, Mubashar F, Siegfried H, Victor K, Ellison D, Jarman RG, Biswal S, Wallace D, Dean H, Tricou V, Currier JR. Cell-mediated immunity generated by Takeda's tetravalent dengue vaccine candidate; American Journal of Tropical Medicine and Hygiene 2020; 103(S5):140	wrong outcome
14	Friberg H, Martinez LJ, Lin L, Blaylock JM, De La Barrera RA, Rothman AL, Putnak JR, Eckels KH, Thomas SJ, Jarman RG, Currier JR. Cell-mediated immunity generated in response to a purified inactivated vaccine for dengue virus type 1; mSphere 2020; 1 doi: 10.1128/MSPHERE.00671-19	wrong intervention
15	Goh CB, Brett J, Wallace D, Borkowski A, Dean H. Takeda's candidate Tetravalent Dengue Vaccine (TDV) - Progress to Phase 3; International Journal of Antimicrobial Agents 2017; 50:36	wrong study design
16	Guy B. Combine two different dengue vaccines could efficiently target dengue-naive subjects. Comment to Macias A, Ruiz-Palacios G, Ramos-Castaneda J. Combine dengue vaccines to optimize effectiveness; Vaccine 2020; 38(31):4801-4804; doi: 10.1016/j.vaccine.2020.08.075	wrong study design
17	Hilgenfeld R, Vasudevan SG. Preface 2018; 1062:v-vi	wrong study design
18	Kirkpatrick BD, Whitehead SS, Pierce KK, Tibery CM, Grier PL, Hynes NA, Larsson CJ, Sabundayo BP, Talaat KR, Janiak A, Carmolli MP, Luke CJ, Diehl SA, Durbin AP.	wrong intervention

	The live attenuated dengue vaccine TV003 elicits complete protection against dengue in a human challenge model; Science Translational Medicine 2016; 8(330) doi: 10.1126/scitranslmed.aaf1517	
19	Kuehn BM. Dengue Vaccine Protects Youth, JAMA 2020; 323(3): 209 doi: 10.1001/jama.2019.21234	wrong study design
20	Michlmayr D, Andrade P, Narvekar P, Sharmna M, Dean H, Harris E. Type-specific and cross-reactive b cell responses elicited by a live-attenuated tetravalent dengue vaccine, American Journal of Tropical Medicine and Hygiene 2019; 101(5):454 doi: 10.4269/ajtmh.abstract2019	wrong outcome
21	Michlmayr D, Andrade P, Nascimento EJM, Parker A, Narvekar P, Dean HJ, Harris E. Characterization of the Type-Specific and Cross-Reactive B-Cell Responses Elicited by a Live-Attenuated Tetravalent Dengue Vaccine; J Infect Dis 2021; 223(2):247-257 doi: 10.1093/infdis/jiaa346	wrong outcome
22	Nascimento EJM, Norwood B, Kpamegan E, Parker A, Fernandes J, Perez-Guzman E, Tricou V, Braun R, Sharma M, Dean HJ. Antibodies Produced in Response to a Live-Attenuated Dengue Vaccine are Functional in Activating the Complement System; J Infect Dis 2022 doi: 10.1093/infdis/jiac476	wrong outcome
23	Patel SS, Rauscher M, Kudela M, Pang H. Clinical Safety Experience of TAK-003 for Dengue Fever: a new Tetravalent Live Attenuated Vaccine Candidate; Clin Infect Dis 2022; 76(3):e1350-e1359 doi: 10.1093/cid/ciac418	wrong study design
24	Pinheiro JR, Camilo Dos Reis E, Souza RS, Rocha ALS, Suesdek L, Azevedo V, Tiwari S, Rocha BGS, Birbrair A, Méndez EC, Luiz WB, Amorim JH. Comparison of Neutralizing Dengue Virus B Cell Epitopes and Protective T Cell Epitopes With Those in Three Main Dengue Virus Vaccines; Front Immunol 2021; 12:715136 , doi: 10.3389/fimmu.2021.715136	wrong outcome
25	Sharma M, Glasner DR, Watkins H, Puerta-Guardo H, Kassa Y, Egan MA, Dean H, Harris E. Magnitude and Functionality of the NS1-Specific Antibody Response Elicited by a Live-Attenuated Tetravalent Dengue Vaccine Candidate; J Infect Dis 2020; 221(6):867-877 doi: 10.1093/infdis/jiz081	wrong outcome
26	Swanstrom JA, Henein S, Plante JA, Yount BL, Widman DG, Gallichotte EN, Dean HJ, Osorio JE, Partidos CD, De Silva AM, Baric RS. Analyzing the Human Serum Antibody Responses to a Live Attenuated Tetravalent Dengue Vaccine Candidate; J Infect Dis 2018; 217(12):1932-1941 doi: 10.1093/infdis/jiy063	wrong outcome
27	Tricou V, Biswal S, Liu M, Patel SS, Zent O, Rauscher M, Perez G, Kandeil W, Folschweiller N. Tetravalent Dengue Vaccine (TAK-003) Development Program: A Bird's Eye View; Open Forum Infectious Diseases 2021 8(S1):S61 doi: 10.1093/ofid/ofab466.097	insufficient data for extraction
28	Tricou V, Gottardo R, Egan MA, Clement F, Leroux-Roels G, Sáez-Llorens X, Borkowski A, Wallace D, Dean HJ. Characterization of the cell-mediated immune response to Takeda's live-attenuated tetravalent dengue vaccine in adolescents participating in a phase 2 randomized controlled trial conducted in a dengue-endemic setting; Vaccine 2022; 40(8):1143-1151	wrong intervention
29	Tricou V, Low JG, Oh HM, Leo YS, Kalimuddin S, Wijaya L, Pang J, Ling LM, Lee TH, Brose M, Hutagalung Y, Rauscher M, Borkowski A, Wallace D. Safety and immunogenicity of a single dose of a tetravalent dengue vaccine with two different serotype-2 potencies in adults in Singapore: A phase 2, double-blind, randomised, controlled trial; Vaccine 2020; 38(6):1513-1519; doi: 10.1016/j.vaccine.2019.11.061	wrong intervention
30	Tricou V, Sáez-Llorens X, Yu D, Rivera L, Borkowski A, Wallace D. Progress in development of Takeda's tetravalent dengue vaccine candidate; American Journal of Tropical Medicine and Hygiene 2017; 97(5):194	wrong study design
31	Tricou V, Sáez-Llorens X, Yu D, Rivera L, Borkowski A, Wallace D. Immunogenicity and safety of Takeda's dengue vaccine candidate in children and adolescents aged 2-17 years from panama, the dominican republic and the philippines: 18-month results from a phase 2 randomized placebo-controlled trial, American Journal of Tropical Medicine and Hygiene 2017; 97(5):252-253	wrong study design
32	Turner M, Papadimitriou A, Winkle P, Segall N, Levin M, Doust M, Johnson C, Lucksinger G, Fierro C, Pickrell P, Raanan M, Tricou V, Borkowski A, Wallace D Immunogenicity and safety of lyophilized and liquid dengue tetravalent vaccine candidate formulations in healthy adults: a randomized, phase 2 clinical trial; Human Vaccines and Immunotherapeutics 2020; 16(10):2456-2464	wrong study design
33	Wallace D, Tricou V, Stinchcomb D, Amfo K, Borkowski A. Takeda's tetravalent dengue vaccine (TDV) candidate progresses to phase iii: Safety and	wrong study design

	immunogenicity of TDV; American Journal of Tropical Medicine and Hygiene 2016; 95(5):20 doi: 10.4269/ajtmh.abstract2016	
34	White L J, Stoops M, Swanstrom J, Young E, Mukherjee S, Dean H, Baric RS, De Silva AM. Quality of the antibody response induced by a live attenuated tetravalent dengue vaccine in naive and dengue exposed individuals; American Journal of Tropical Medicine and Hygiene 2018; 99(4):506-507	wrong study design
34	White LJ, Young EF, Stoops MJ, Henein SR, Adams EC, Baric RS, de Silva AM. Defining levels of dengue virus serotype-specific neutralizing antibodies induced by a live attenuated tetravalent dengue vaccine (Tak-003); PLoS Neglected Tropical Diseases 2021; 15(3) doi: 10.1371/journal.pntd.0009258	wrong intervention

5. Evidence-to-Decision-Tabelle

Soll die Impfung mit Qdenga (2 Impfstoffdosen im Abstand von 3 Monaten) Reisenden aus Deutschland vor Exposition in einem Dengue-Endemiegebiet empfohlen werden, um Dengue-Infektionen, schwere Dengue-Verläufe und Tod zu verhindern? (Shall vaccination with Qdenga (2 doses given 3 months apart) be recommended for travellers from Germany before exposure to DENV in Dengue-endemic areas?)

Goal of vaccination: Reduction of VCD and severe dengue in travelers.

Criteria		Judgments	Research evidence	Additional considerations
Problem	Is the problem a priority?	o No o Probably no o **Uncertain** o Probably yes o Yes o Varies	Dengue is a vector-borne disease that causes mild disease in most cases. Severe courses of disease, which present with severe plasma leakage, severe haemorrhage and/or severe organ impairment, are rare, but can be fatal. The risk for severe dengue is especially high in secondary infections (published estimates range from relative risk 2,7-9,4 (1, 2). About 3.9 billion people, i.e. approx. 50% of the human population, are exposed to the dengue virus (DENV) (3). The number of dengue cases reported to the WHO has increased more than tenfold over the past two decades (2000: 505,430 cases; 2019: 5.2 million) (4). DENV causes a high burden of disease in endemic countries. Among travelers, dengue is a leading cause of febrile illness returning from Southeast Asia, Latin America, and the Caribbean and is more common than many other travel-related vaccine-preventable diseases. The estimated incidence of symptomatic cases among travelers is 0.2-1.3% per month of travel in non-immune individuals (5-7). Severe cases among travelers are very rare (8). In Germany dengue cases among travelers reported to the Robert Koch Institute increased in past years (2017: 635 cases; 2019: 1.176 cases). The vast majority of these cases showed a mild course of disease (reported hospitalised cases 2017: 5/635, 2019: 3/1176). Pre-conditions that could indicate a possible higher risk for a severe course of disease could not be identified. In the literature considered the conditions or its severity were not consistently defined so that no consistent conclusions could be taken from.	The number of dengue cases reported among travellers in Germany is most probably underestimated, as only those cases are reported that occur in Germany. A relevant number of people may get symptomatic and seek medical therapy outside Germany. These cases are not reported to RKI. Depending on the stated vaccination goal, there are different views with regard to priority of the problem. If infections are to be prevented regardless of severity, vaccination is given a higher priority than if only severe cases are to be prevented, which tend to be very rare among travelers.

<table>
<tr>
<td rowspan="2">Benefits and harms of the options</td>
<td>What is the overall certainty of this evidence?</td>
<td>○ No included studies
○ Very low
○ Low
○ Moderate
○ High</td>
<td>
<table>
<tr><th>Outcome</th><th>Relative importance</th><th>GRADE</th></tr>
<tr><td>VE</td><td></td><td></td></tr>
<tr><td>Virologically Confirmed Dengue (VCD)</td><td>critical</td><td>Low to very low</td></tr>
<tr><td>Severe dengue according to WHO definition (2009)</td><td>critical</td><td>Very low</td></tr>
<tr><td>Safety</td><td></td><td></td></tr>
<tr><td>Local and systemic reactions</td><td>important</td><td>Low</td></tr>
<tr><td>Fever</td><td>important</td><td>Very low</td></tr>
<tr><td>SAE incl. death</td><td>important</td><td>Very low</td></tr>
</table>
</td>
<td>The study population in the included studies differed from the population of German travelers. The study with the largest number of participants (>20,000) included only participants between 4-16 years of age with 72% being seropositive before vaccination.</td>
</tr>
<tr>
<td>Is there important uncertainty about how much people value the main outcomes?</td>
<td>○ Important uncertainty or variability
○ Possibly important uncertainty or variability
○ Probably no important uncertainty or variability
○ No important uncertainty or variability
○ No known undesirable outcomes</td>
<td>There are no data available of the uncertainty about the main outcomes among travelers. It is assumed that travelers value the safety of the vaccine and the prevention of VCD, and severe dengue as very important outcomes.</td>
<td></td>
</tr>
</table>

<table>
<tr>
<td></td>
<td>Are the desirable anticipated effects large?</td>
<td>○ No
○ Probably no
○ Uncertain
○ Probably yes
○ Yes
○ Varies</td>
<td><u>Vaccine efficacy (VE)</u>:
Overall VE against virologically confirmed dengue (VCD) was demonstrated in a large phase 3 randomised controlled trail (VE up to 18 months after 2. dose: 80.2%, 95% confidence interval (95% CI) 73.3-85.3, TIDES-study).
VE declined over time (VE up to 3 years after 2nd dose: 62.0% (95% CI: 56.6-66.7). However, VE varied by baseline serostatus and infecting DENV serotype.

VE (%) against VCD over time by baseline serostatus (95% CI)
<table>
<tr><td></td><td>≤ 18 months</td><td>≤ 2 years</td><td>≤ 3 years</td></tr>
<tr><td>Overall</td><td>80,2 %
(75,2 – 85,3)</td><td>72,7 %
(67,1 – 77,3)</td><td>62,0 %
(56,6–66,7)</td></tr>
<tr><td>Baseline seropositive</td><td>81,9 %
(75,3- 86,7)</td><td>74,8 %
(68,6 – 79,8)</td><td>65,0 %
(58,9–70,1)</td></tr>
<tr><td>Baseline seronegative</td><td>78,5 %
(65,0 – 86,9)</td><td>67,0 %
(53,6 – 76,5)</td><td>54,3 %
(41,9–64,1)</td></tr>
</table>
VE against VCD was significantly higher in individuals who were seropositive at baseline than in seronegative individuals. In seronegatives at baseline, the 95% confidence interval of VE for DENV-1 at year 3, for DENV-2 at year 2, and for DENV-3 and DENV-4 at years 1, 2, and 3 yields both the possibility of relevant benefit and harm or null effect. The current data could not demonstrate VE against severe dengue due to the small number of cases (VE against severe dengue ≤ 18 months after 2nd dose: 50.2% (-696.1–96.9).
<u>Immunogenicity</u>: The GMT reported over time showed that their levels dropped after two vaccine doses in the first six months after the 2nd dose of vaccine, but then stabilized at one level over time. GMT for DENV-2 were higher than GMT for the other serotypes over the entire 3-year period. The level of GMT for seropositives was higher than those for seronegatives (9).
An immunobridging study compared immunogenicity parameters of pre-vaccine seronegative 4- to 16-year-old children and adolescents from endemic countries with those of seronegative 18- to 60-year-old adults from the US. GMT ratios were comparable at 4 and 9 months after administration of the 1st vaccine dose, allowing transferability of immunogenicity data</td>
<td>Since there are no reliable incidence data among travelers, a number needed to vaccinate cannot be determined.

The definition of severe dengue used in the studies did not fully match the definition of the WHO 2009 that we used for the defined outcome of severe dengue.

Since there is no seroimmunological correlate for protection, the immunogenicity data were only used to support the VE data.</td>
</tr>
</table>

			from seronegative children in endemic countries to seronegative adults in non-endemic countries (10).	
	Are the undesirable anticipated effects small?	○ No ○ Probably no ○ Uncertain ○ **Probably yes** ○ Yes ○ Varies	Based on the current data the vaccine was well tolerated. However, local reaction (pain, redness, swelling) up to 7 days after vaccination and systemic reaction up to 14 days after vaccination occurred more often in the intervention group than in the placebo group (< 6 years of age: 32.02% vs 25.44% resp. 26.59% vs 20.71%; ≥ 6 years of age: 37,40% vs 25.70% resp. 40.88% vs 36.9%). Based on the current data the theoretic risk of an enhanced disease in baseline seronegative individuals cannot be ruled out. The ADE-risk has been observed in another live-attenuated dengue vaccine.	
	Are the desirable effects large relative to undesirable effects?	○ No ○ Probably no ○ Uncertain ○ Probably yes ○ Yes ○ **Varies**	In baseline seropositives, the desirable effects outweigh probable harms. In baseline seronegatives, the wide VE confidence interval against severe disease may include both a benefit from vaccination as well as a risk from vaccination due to a potential risk of a severe course of disease.	
Resource use	Are the resources required small?	○ No ○ **Probably no** ○ Uncertain ○ Probably yes ○ Yes ○ Varies	No cost effectiveness analysis was performed. The costs for vaccinations are relatively high (2 doses ca. 250 €).	
	Is the incremental cost small relative to the net benefits?	○ No ○ Probably no ○ Uncertain ○ Probably yes ○ Yes ○ Varies		

Equity	What would be the impact on health inequities?	○ Increased ○ **Probably increased** ○ Uncertain ○ Probably reduced ○ Reduced ○ Varies	Travel vaccinations are not always covered by health insurance. Therefore, there might be an inequity in persons who can afford the vaccine and others who cannot.	
Acceptability	Is the option acceptable to key stakeholders?	○ No ○ Probably no ○ **Uncertain** ○ Probably yes ○ Yes ○ Varies	It is assumed that the vaccine will be acceptable for stakeholders, but might depend on the level of explanation that is given in regard to the VE data and the uncertainty about the risk of a second infection.	
Feasibility	Is the option feasible to implement?	○ No ○ Probably no ○ **Uncertain** ○ Probably yes ○ Yes ○ Varies	- The vaccination schedule includes a minimum interval of 3 months between doses. Travel vaccination counselling is often only done shortly before the start of the trip. Completion of the vaccination series before travelling is therefore most probably not feasible. The vaccination schedule is especially impractical for short-term travelers. Data on efficacy after one vaccine dose are so far only available up to a period of 3 months. - Study data demonstrates possible coadministration with live-attenuated yellow fever vaccine and inactivated hepatitis A vaccine. Coadministration studies with other vaccines are currently ongoing.	

Recommendation	**Shall vaccination with Qdenga (2 doses given 3 months apart) be recommended for travelers from Germany before exposure to DENV in dengue-endemic areas?**				
Balance of consequences	Undesirable consequences clearly outweigh desirable consequences	Undesirable consequences probably outweigh desirable consequences	**The balance between desirable and undesirable consequences is closely balanced or uncertain**	Desirable consequences probably outweigh undesirable consequences	Desirable consequences clearly outweigh undesirable consequences
	○	○	○	○	○
Recommendation	Vaccination against dengue with the vaccine Qdenga is recommended for persons aged 4 years and older who anamnestically report to have had a laboratory-confirmed DENV infection in the past and are traveling to a dengue endemic area where they have an increased risk of exposure (e.g., prolonged stay, current outbreak). Before travel a full vaccination series should be applied. The vaccine may be considered on an individual level in travelers without previous DENV infection after medical consultation and in line with the vaccine approval. In these cases, a complete vaccination series is recommended before departure (i.e. 2 vaccine doses at a minimum interval of 3 months).				

Justification	The risk for severe dengue is higher in a secondary infection than with an initial infection. To date, it cannot be ruled out that travelers without a prior DENV infection have an increased risk of a severe course of disease with possible fatal consequences following vaccination and subsequent contact with the virus.
Subgroup considerations	The vaccination is contraindicated in pregnant and breast-feeding women and in persons with immunodeficiencies.
Implementation considerations	Coadministration with yellow fever and hepatitis A vaccines is possible. Vaccination recommendations must be well accompanied by communication, because unlike other vaccinations, it is counterintuitive to vaccinate primarily people who have already been through an illness and to let people without prior wild virus contact first go through the usually harmless infection before vaccination. The acceptance in stakeholders and also in travelers will depend on the level of explanation that is given in regard to the VE data and the uncertainty about the risk of a second infection.
Monitoring and evaluation	- Surveillance of Pau-Ehrlich-Institute (PEI) for safety signals of Qdenga - Collection of safety data by the multicentric surveillance study initiated by Homburg university - Close monitoring of serotype distribution in ill returned travelers
Research priorities	- A study to investigate the possible risk of enhanced disease after vaccination in seronegatives - Additional studies on the VE, especially to confirm protection against DENV3 and DENV4 - Publication of study data for 54 months investigating duration of protection of Qdenga - Data on booster vaccinations - Coadministration studies with other vaccines than yellow fever and hepatitis A - VE studies in seronegative travelers - Safety data stratified by serostatus

6. Literatur zum Anhang

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