XI Ad Hoc Meeting of the PAHO Technical Advisory Group (TAG) on Vaccine-Preventable Diseases

21 November 2023
Virtual

PAHO Pan American Health Organization
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Washington, D.C., 2023
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Abbreviations and acronyms

BLA biologics license application
CI confidence interval
DCAC Dengue Case Adjudication Committee
DENV dengue virus
DHF dengue hemorrhagic fever
DTP3 diphtheria, tetanus, and pertussis, third dose
EMA European Medicines Agency
EW epidemiological week
FDA U.S. Food and Drug Administration
GMT geometric mean titer
HIC high-income countries
ICU intensive care unit
ILI influenza-like illness
LMIC lower-middle-income countries
LRTD lower respiratory tract disease
mAb monoclonal antibody
PAHO Pan American Health Organization
RSV respiratory syncytial virus
RSVpreF RSV prefusion F
RT-PCR reverse-transcriptase polymerase chain reaction
SAGE Strategic Advisory Group of Experts
SARI severe acute respiratory infections
SP9 seroprevalence at 9 years of age
TAG Technical Advisory Group
TAK-003 Takeda’s tetravalent dengue vaccine
Tdap tetanus–diphtheria–pertussis vaccine
TDV tetravalent dengue vaccine
UMIC upper middle-income countries
VCD virologically confirmed dengue
VE vaccine efficacy
WHO World Health Organization
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Background

Slowly, the Region of the Americas is recovering its immunization coverage rates for most antigens. In 2022, the coverage rate for the third dose of the vaccine against diphtheria, tetanus, and pertussis (DTP3) was 90% – up from 86% in 2021. Overall, 1.3 million children younger than 1 year remain unvaccinated, compared to 1.9 million in 2021. Of course, the road to recovery from the COVID-19 pandemic is long, but the Americas are showing signs of progress.

However, this progress is under threat from persistent infections that cause heavy burdens of disease in the Americas. Especially heavy is the burden of dengue virus. In 2002, dengue cases exceeded 1 million, whereas more than 2 million were recorded in 2013, and more than 3 million in 2019. While the regional dengue case fatality rate remains below 0.05%, the increased transmission is undermining countries' efforts for social and economic recovery. In September 2023, the World Health Organization (WHO) Strategic Advisory Group of Experts (SAGE) on Immunization recommended the use of the two-dose TAK-003 dengue vaccine series produced by Takeda for children ages 6 to 16 years who live in settings with high dengue disease burden and high transmission intensity. During this XI Technical Advisory Group (TAG) meeting, the Pan American Health Organization (PAHO) Secretariat asked TAG members to consider the evidence on the safety and effectiveness of this vaccine and propose recommendations for its use in the Americas.

Also, respiratory syncytial virus (RSV) is cause for great concern in the Americas. Data reported from Member States to the PAHO integrated respiratory surveillance network SARInet Plus indicate that RSV contributes significantly to the burden of respiratory diseases in the Region. By age group, RSV-associated cases and hospitalizations have been primarily reported among infants younger than 2 years. In recent months, both the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approved the RSVpreF vaccine Abrysvo produced by Pfizer for pregnant women, with the goal of reducing RSV incidence among newborns younger than 6 months. Again, TAG members were called to provide their recommendations to PAHO on the use of this vaccine in the Americas.
Vaccine against dengue virus

Question for the TAG

• Should the countries of the Americas with a high burden and high transmission intensity of dengue disease consider the introduction of the TAK-003 vaccine against dengue?

Dengue epidemiology update in the Region of the Americas

Despite the constant efforts made by countries to prevent and control dengue, the trend in the number of dengue cases in the Region of the Americas is increasing. In the 1980s, 1.6 million cases were reported, and this number doubled in the following decade (3.1 million cases). In the 2000s, there were 7.8 million cases, and these more than doubled in the 2010s, to 18.2 million cases. In the last three years, 7.6 million cases have been reported.

Years with dengue epidemics increasingly outnumber those that preceded them. For example, in 2002, dengue cases exceeded 1 million at the regional level; then, in 2013 more than 2 million cases were recorded for the first time, and in 2019 more than 3 million cases were recorded. To date, 2023 is the year with the highest record of dengue cases in the Region, with 3.6 million cases (Figure 1). Dengue epidemics occur cyclically, with a combination of factors related to mosquito density, simultaneously circulating serotypes or introduction of new serotypes, and the accumulation of susceptible people. The four dengue serotypes are widely distributed in the Americas, and the simultaneous circulation of two or more serotypes is currently observed in many countries. Figure 2 shows how the four dengue serotypes have spread to more countries in the Americas over time, which introduces a greater degree of complexity to the clinical–epidemiological pattern in the Region.

1 Most of the information presented in this report has been obtained from: “Meeting of the Strategic Advisory Group of Experts on Immunization, September 2023: conclusions and recommendations.” Available from: https://iris.who.int/bitstream/handle/10665/374327/WER9847-eng-fre.pdf?sequence=1
Figure 1. Number of dengue cases* in the Americas, 1981–2023

<table>
<thead>
<tr>
<th>Region of the Americas</th>
<th>Suspected</th>
<th>Cumulative Incidence*</th>
<th>Confirmed</th>
<th>Severe Dengue</th>
<th>Deaths</th>
<th>Lethality**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 2023</td>
<td>4,071,319</td>
<td>409</td>
<td>1,834,744 (45%)</td>
<td>6,241</td>
<td>1,910</td>
<td>0.047</td>
</tr>
</tbody>
</table>

Source: Health Information Platform (PLISA), PAHO.
* Per 100,000 inhabitants/ ** Per 100 cases
& In dengue, all clinically suspected cases are reported.

Figure 2. Severe dengue in the Americas, 1995–2010–2023

Source: Health Information Platform (PLISA), PAHO.

Unlike the increase observed in the number of dengue cases, the severity and fatality of this disease have shown a trend toward decrease. On average, the proportion of serious dengue cases in the Americas in the last 10 years is 0.85% and the fatality rate has remained below 0.05%. In
2009, WHO published an update of the clinical management guidelines for dengue in which a new classification of dengue severity was proposed, moving from the concept of dengue hemorrhagic fever and dengue shock syndrome to dengue with or without warning signs, and severe dengue. The new clinical classification allows, through clinical alarm signs, early identification of the patients who are progressing to severity and thus action to be taken to prevent this. This classification and the clinical approach focused on primary health care began to be implemented in the Americas in 2010, and since then a positive impact has been observed in reducing serious illnesses and deaths from dengue (Figure 2).

**Dengue trend 2023**

As of epidemiological week (EW) 40 of 2023, 3,587,798 suspected cases of dengue have been registered in the Americas, for a regional cumulative incidence of 361 cases per 100,000 population. Figure 3 shows the countries with the highest number of suspected dengue cases and the countries with the highest cumulative incidence (per 100,000 population) of the disease.

**Figure 3. Number of cases and cumulative incidence* of dengue by country, epidemiological week 40-2023**

<table>
<thead>
<tr>
<th>Countries/territories</th>
<th>DENV1</th>
<th>DENV2</th>
<th>DENV3</th>
<th>DENV4</th>
</tr>
</thead>
</table>

*Note: *Per 100,000 population.

*Source: Health Information Platform (PLISA), PAHO.*

The percentage of laboratory confirmation varies from country to country. However, all countries in the Americas have installed capacity for the molecular and serological diagnosis of dengue. Of the total suspected cases at the regional level, 46% (1,653,870) have been laboratory-confirmed. Among countries with the highest number of cases, the percentage of laboratory confirmation of dengue until EW 40 of 2023 is: Argentina (100%), Bolivia (Plurinational State of) (16%), Brazil (46%), Colombia (62%), Mexico, (18%), Nicaragua (4%), and Peru (71%). All four serotypes of the virus are currently circulating in the Americas. In 2023, a total of five countries have reported simultaneous circulation of the four dengue serotypes (Table 1).

**Table 1. Proportion of dengue serotypes in six countries and one territory of the Americas, epidemiological week 40-2023**
<table>
<thead>
<tr>
<th>Country</th>
<th>14.5%</th>
<th>85.4%</th>
<th>0.06%</th>
<th>0.001%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argentina</td>
<td>25%</td>
<td>18%</td>
<td>22%</td>
<td>35%</td>
</tr>
<tr>
<td>Guatemala</td>
<td>15%</td>
<td>29%</td>
<td>49%</td>
<td>8%</td>
</tr>
<tr>
<td>Honduras</td>
<td>25%</td>
<td>5%</td>
<td>38%</td>
<td>32%</td>
</tr>
<tr>
<td>Mexico</td>
<td>16.7%</td>
<td>22.4%</td>
<td>58.5%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Paraguay</td>
<td>50.1%</td>
<td>49.9%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Puerto Rico</td>
<td>74.2%</td>
<td>23%</td>
<td>2.8%</td>
<td>0</td>
</tr>
</tbody>
</table>

Source: PAHO. Data provided by the institutes and ministries of health of the countries.

In relation to cases of severe dengue, 5602 serious cases were registered in 2023, which represents 0.16% of the total suspected cases. The five countries with the highest number of serious cases are Brazil (1396 cases), Colombia (1309), Peru (999), Mexico (768), and Bolivia (Plurinational State of) (627). The regional fatality rate for this year is 0.049%. The five countries with the highest number of deaths are Brazil (912), Peru (424), Bolivia (Plurinational State of) (83), Colombia (71), and Argentina (65).

Not all countries have reported their cases by age group to PAHO, which is why a regional analysis by age group cannot be carried out. However, this information is available from Argentina, Brazil, Mexico, Paraguay, and Puerto Rico. The incidence of dengue by age group varies from country to country. For example: in Argentina the highest cumulative incidence of dengue is in the 25–29 years age group; in Brazil the highest incidence is in the 20–24 age group; in Mexico and Puerto Rico it is in the 10–14 age group; and in Paraguay it is in the group aged 80 years and older.

**Dengue virus infection characteristics**

First (or primary) infection with any of the four dengue virus (DENV) serotypes leads to the induction of type-specific antibodies that provide long-lasting protection against reinfection with the same serotype and short-lasting cross-protection against other serotypes. Primary infections are generally asymptomatic or cause relatively mild clinical symptoms, although they can sometimes cause severe disease. Subsequent infection with another DENV serotype (secondary infection) is more likely to be associated with the occurrence of severe disease, while a third or fourth infection with a further DENV serotype is usually either asymptomatic or associated with mild disease. In most dengue-endemic countries all four DENV serotypes have been reported, although at any one time a single serotype usually predominates (or sometimes two predominate).

**TAK-003 vaccine characteristics**

Takeda’s tetravalent dengue vaccine (TAK-003) is live-attenuated. A live-attenuated dengue serotype 2 virus (DENV2) strain (TDV-2), originally isolated in Thailand in 1964 (DENV2 PDK53), provides the genetic backbone of the vaccine (1). The other three vaccine strains (TDV-1, TDV-3, and TDV-4) are chimeric strains that were generated by replacing the envelope (E) and pre-membrane (prM) genes of TDV-2 with those from wild-type dengue virus type 1 (DENV1), type 3 (DENV3), and type 4 (DENV4) strains. The vaccination schedule for the primary series is two doses administered subcutaneously with an interval of three months between doses.
TAK-003 Phase 3 clinical trials

The Phase 3 efficacy trial for the live attenuated tetravalent dengue vaccine, TAK-003 (Qdenga®), was conducted over almost five years in children and adolescents (4–16 years of age) residing in dengue-endemic countries in Asia and Latin America. The dengue seroprevalence (the percentage of dengue seropositive persons) in the study population prior to vaccination was on average around 70% (range 38–97%), and the dominant circulating strains were serotypes 1 and 2. In these study populations and study settings, the overall vaccine efficacy (VE) of TAK-003 over five years against virologically confirmed dengue (VCD) was 61% (95% CI [56.0, 65.8]) and against dengue-related hospitalizations 84% (77.8, 88.6).

VE against dengue-related hospitalizations was higher compared to that against VCD. VE varied by serostatus and serotype, with higher VE in persons with a baseline seropositive serostatus (persons who have had one or more previous dengue infections) compared to those with baseline seronegative serostatus (without prior dengue infection). VE was the highest against DENV2, both in seropositive and seronegative persons.

In baseline seropositive persons, TAK-003 was safe and efficacious against all four DENV serotypes both for VCD and hospitalizations, with the highest protection against DENV2. In baseline seronegative persons, the vaccine provided protection against DENV1 and very high protection against DENV2, both for VCD and hospitalizations. However, the vaccine did not provide any protection against VCD and hospitalizations due to DENV3, nor did it provide protection against VCD due to DENV4. The number of cases of DENV4-associated hospitalizations in the trial was too few to estimate efficacy against DENV4 hospitalizations in seronegative persons.

The large pivotal Phase 3 trial involving about 20 000 children was not sufficiently powered to definitively rule out a risk of vaccine-enhanced disease in baseline seronegative persons exposed after the vaccination to DENV3 and DENV4, as the number of cases due to DENV3 and DENV4 was relatively small during the trial period. In this subgroup of baseline seronegative children there were higher rates of VCD as well as hospitalized DENV3 cases and severe dengue cases, among vaccinated persons than among seronegative unvaccinated persons, but this excess was small and not statistically significant. WHO acknowledges that vaccine-enhanced disease in a subpopulation of seronegative persons exposed to DENV3 and possibly DENV4 is biologically plausible and cannot be ruled out from the results of the Phase 3 trial.

TAK-003 vaccine efficacy data

Study design and methods

Healthy children and adolescents ages 4–16 years (N = 20 099) were randomized 2:1 to receive TAK-003 or placebo (0, 3-month schedule). Subjects were enrolled at 26 sites in eight dengue-endemic countries in Asia and Latin America. Those countries in the Americas are Brazil, Colombia, Dominican Republic, Nicaragua, and Panama; the countries in Asia are Philippines, Sri Lanka, and Thailand. The number of participants from the Americas was 10 183 children: 6808 in
the vaccinated group and 3375 in the placebo group (2:1 ratio). Only middle- or high-income countries participated in the study.

The primary endpoint was overall vaccine efficacy in preventing VCD caused by any dengue virus serotype from 30 days to 12 months after the second dose. Secondary endpoints included efficacy against VCD requiring hospitalization, VCD stratified by serotype and baseline serostatus, and severity of disease 30 days to 18 months after the second dose (2). The severity of VCD was assessed using two approaches: (1) masked review by the Dengue Case Adjudication Committee (DCAC) using predefined criteria; and (2) by an algorithm developed by the study statisticians to analyze data according to the WHO 1997 dengue hemorrhagic fever criteria. Participants presenting with febrile illness were tested for virological confirmation of dengue by serotype-specific reverse-transcriptase polymerase chain reaction (RT-PCR).

Active surveillance with at least weekly contact was conducted to identify all febrile illnesses, irrespective of the need for hospitalization, during the first two phases of the trial (i.e., up to 18 months after the second dose of vaccination). During the third phase, modified active surveillance was conducted wherein laboratory confirmation by RT-PCR was conducted only on hospitalized febrile illnesses and non-hospitalized febrile illnesses where no alternative cause for the fever was identified.

The protocol included baseline serostatus testing of all participants. Baseline seropositivity was defined as a microneutralization (MNT) titer of ≥10, which was the limit of detection by the assay used and not a correlate of protection. Seropositivity against other flaviviruses was not assessed. Subset safety assessments included diary-recorded local reactions for 7 days post-vaccination and systemic adverse events for 14 days post-vaccination and unsolicited adverse events for 28 days post-vaccination. Serious adverse events and adverse events leading to withdrawal from the study were collected for all study participants for the duration of the trial.²

**Efficacy of the TAK-003 vaccine against symptomatic infection of virologically confirmed dengue (VCD)**

Vaccine efficacy against primary and secondary endpoints per protocol set data showed an efficacy of 80% against VCD and 90% against hospitalization (Figure 4). Vaccine efficacy after the first dose was 81.1% (95% CI [64, 90]), indicating rapid onset of protection. The efficacy estimates were similar between baseline seropositive subjects (VE 79%; 95% CI [55, 90]) and baseline seronegative subjects (VE 87%; 95% CI [52, 96]). Among the VCD cases between the first and second doses, eight were hospitalized – six in the placebo group, and two in the vaccine group (Figure 4). During the extended follow-up period (57 months following the first dose), overall VE against VCD was 61.2% (95% CI [56.0, 65.8]) and against hospitalization was 84.1% (95% CI [77.8, 88.6]).

² The WHO guidelines did not define vaccine-enhanced severe dengue disease as a “serious adverse event” (SAE). These events are rather presented as negative efficacy. No adverse events were attributed to breakthrough DENV infections.
Figure 4. Efficacy of the TAK-003 vaccine against the primary and secondary clinical endpoints

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Placebo (n=317)</th>
<th>TAK-003 (n=1,270)</th>
<th>VE</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 days to 12 months post 2nd dose (primary endpoint)</td>
<td>140 (2.0)</td>
<td>62 (0.5)</td>
<td>80.2</td>
<td>(72.3, 85.3)</td>
</tr>
<tr>
<td>VCD by any serotype</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline seropositive</td>
<td>66 (0.8)</td>
<td>13 (0.1)</td>
<td>98.4</td>
<td>(92.0, 99.7)</td>
</tr>
<tr>
<td>VCD by any serotype</td>
<td>206 (2.4)</td>
<td>14 (0.1)</td>
<td>93.3</td>
<td>(90.5, 95.0)</td>
</tr>
<tr>
<td>Baseline seronegative</td>
<td>51 (0.5)</td>
<td>3 (0.0)</td>
<td>94.1</td>
<td>(90.5, 96.1)</td>
</tr>
<tr>
<td>VCD by DENV-1</td>
<td>62 (0.2)</td>
<td>38 (0.3)</td>
<td>90.3</td>
<td>(84.8, 94.4)</td>
</tr>
<tr>
<td>VCD by DENV-2</td>
<td>80 (0.9)</td>
<td>8 (0.1)</td>
<td>93.7</td>
<td>(89.9, 97.6)</td>
</tr>
<tr>
<td>VCD by DENV-3</td>
<td>60 (0.7)</td>
<td>63 (0.7)</td>
<td>97.9</td>
<td>(93.4, 99.7)</td>
</tr>
<tr>
<td>VCD by DENV-4</td>
<td>5 (0.1)</td>
<td>5 (0.1)</td>
<td>99.0</td>
<td>(95.4, 100.0)</td>
</tr>
<tr>
<td>DCM-defined severe VCD</td>
<td>1 (0.1)</td>
<td>2 (0.1)</td>
<td>80.0</td>
<td>(1.4, 99.7)</td>
</tr>
<tr>
<td>DHF</td>
<td>7 (0.2)</td>
<td>2 (0.1)</td>
<td>91.9</td>
<td>(47.8, 99.7)</td>
</tr>
</tbody>
</table>


The vaccine was shown to be efficacious in both seropositive and seronegative individuals over the 57 months of follow-up against both VCD and hospitalized VCD, albeit with slightly lower point estimates of efficacy (with overlapping confidence intervals) in seronegative individuals (Figures 5 and 6).

Figure 5. Cumulative incidence of virologically confirmed dengue (VCD) over 57 months

Figure 6. Cumulative incidence of hospitalized virologically confirmed dengue (VCD) over 57 months


However, efficacy results vary depending on the infecting serotype and baseline serostatus, as described below.

**Efficacy against virologically confirmed dengue (VCD) and hospitalized VCD by baseline serostatus and infecting serotype**

Against VCD, the vaccine was shown to be efficacious against all four serotypes in baseline seropositive subjects. In baseline seronegative subjects, statistically non-significant negative point estimates of efficacy with very wide confidence limits were noted for DENV3 and DENV4 (Table 2).
Table 2. Vaccine efficacy against virologically confirmed dengue (VCD) by baseline serostatus and virus serotype 57 months after the first dose of vaccination (safety dataset)

<table>
<thead>
<tr>
<th>VCD Cases</th>
<th>TAK-003 N = 13,380</th>
<th>Placebo N = 6,687</th>
<th>Favors TAK-003</th>
<th>Vaccine Efficacy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seropositive</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DENV-1</td>
<td>133</td>
<td>151</td>
<td></td>
<td>56.1% (44.6, 65.2)</td>
</tr>
<tr>
<td>DENV-2</td>
<td>54</td>
<td>135</td>
<td></td>
<td>80.4% (73.1, 85.7)</td>
</tr>
<tr>
<td>DENV-3</td>
<td>96</td>
<td>97</td>
<td></td>
<td>52.3% (36.7, 64.0)</td>
</tr>
<tr>
<td>DENV-4</td>
<td>12</td>
<td>20</td>
<td></td>
<td>70.6% (39.9, 85.6)</td>
</tr>
<tr>
<td>Seronegative</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DENV-1</td>
<td>89</td>
<td>79</td>
<td></td>
<td>45.4% (26.1, 59.7)</td>
</tr>
<tr>
<td>DENV-2</td>
<td>14</td>
<td>58</td>
<td></td>
<td>88.1% (78.6, 93.3)</td>
</tr>
<tr>
<td>DENV-3</td>
<td>36</td>
<td>16</td>
<td></td>
<td>-15.5% (-108.2, 35.9)</td>
</tr>
<tr>
<td>DENV-4</td>
<td>12</td>
<td>3</td>
<td></td>
<td>-105.6% (-628.7, 42.0)</td>
</tr>
</tbody>
</table>


Against hospitalized VCD, there were too few cases due to DENV4 in baseline seropositive or seronegative individuals to draw valid conclusions. Among baseline seronegative individuals, a statistically non-significant negative point estimate of efficacy with very wide confidence intervals was observed for DENV3 (Table 3). That negative efficacy of –87.9% represents an excess of risk, even though confidence intervals are not statistically significant.

Table 3. Vaccine efficacy against hospitalized virologically confirmed dengue (VCD) by baseline serostatus and virus serotype 57 months after the first dose of vaccination (safety dataset)

<table>
<thead>
<tr>
<th>Hospitalizations</th>
<th>TAK-003 N = 13,380</th>
<th>Placebo N = 6,687</th>
<th>Favors TAK-003</th>
<th>Vaccine Efficacy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seropositive</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DENV-1</td>
<td>16</td>
<td>24</td>
<td></td>
<td>66.8% (37.4, 82.3)</td>
</tr>
<tr>
<td>DENV-2</td>
<td>5</td>
<td>59</td>
<td></td>
<td>95.8% (89.6, 98.3)</td>
</tr>
<tr>
<td>DENV-3</td>
<td>8</td>
<td>15</td>
<td></td>
<td>74.0% (38.6, 89.0)</td>
</tr>
<tr>
<td>DENV-4</td>
<td>0</td>
<td>3</td>
<td></td>
<td>100% (NE, NE)</td>
</tr>
<tr>
<td>Seronegative</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DENV-1</td>
<td>6</td>
<td>14</td>
<td></td>
<td>78.4% (43.9, 91.7)</td>
</tr>
<tr>
<td>DENV-2</td>
<td>0</td>
<td>23</td>
<td></td>
<td>100% (NE, NE)</td>
</tr>
<tr>
<td>DENV-3</td>
<td>11</td>
<td>3</td>
<td></td>
<td>-87.9% (-573.4, 47.6)</td>
</tr>
<tr>
<td>DENV-4</td>
<td>0</td>
<td>1</td>
<td></td>
<td>100% (NE, NE)</td>
</tr>
</tbody>
</table>

Rates of hospitalization varied considerably between countries, ranging from 4.4% to 68% of all VCD cases. There were no defined thresholds for hospitalization in the context of the study and these decisions were left to the treating clinicians. The highest rate (68%) of hospitalization was observed in Sri Lanka, where all cases with a positive rapid antigen test for the non-structural protein 1 (NS1) of the dengue virus in the serum were hospitalized for observation. Of the 700 individuals in the safety dataset from Sri Lanka, 70 of 103 VCD cases were hospitalized. In contrast, among the 5987 individuals in the safety dataset from the sites in the other countries, only 72 of 457 VCD cases were hospitalized. In addition, platelet counts and ultrasound examinations for plasma leakage were conducted more frequently in Sri Lanka compared to other sites, leading to higher rates of patients classified as dengue hemorrhagic fever (DHF). Hence, a sensitivity analysis was performed with and without hospitalized cases from Sri Lanka. The efficacy against hospitalized VCD with and without Sri Lanka data is shown in Figure 7.

**Figure 7. Efficacy against hospitalized virologically confirmed dengue (VCD) with and without Sri Lanka data by baseline serostatus and virus serotype, 57-month follow-up**

![Graph showing efficacy against hospitalized VCD](source)

The overall efficacy against hospitalized VCD (from all serotypes) was high in baseline seropositive and seronegative individuals with or without Sri Lanka data. Similarly, among baseline seropositive subjects, efficacy was demonstrated in all hospitalized VCD by any serotype as well as for DENV1, DENV2, and DENV3; there was not enough data for DENV4 to allow estimation. Among baseline seronegative subjects, in the stratified analysis on hospitalized VCD by serotype, the point estimate for efficacy against DENV3 changed from a negative (–87.9%) to a positive point estimate (15.3%) when Sri Lanka data were removed, albeit with very wide and overlapping confidence intervals for both estimates. It is also important to note that when removing Sri Lanka, there were not enough cases to estimate the effectiveness for DENV2 in
baseline seronegative children; also, there were not enough cases to estimate effectiveness for DENV4.

Efficacy against severe dengue and dengue hemorrhagic fever (DHF) by baseline serostatus
The efficacy of the vaccine against severe dengue (based on a review by the DCAC) and DHF in the safety dataset with and without Sri Lanka data are shown in Table 4. Overall, the vaccine was efficacious in preventing severe dengue among baseline seropositive individuals (observing a wide confidence interval). In baseline seronegative subjects, the two severe cases were due to DENV3 and there were no severe cases in the placebo group; nevertheless, efficacy calculation was not possible. In baseline seronegative subjects, severe cases were mainly in the 6–8 years age group.

Similarly, the vaccine was shown to be efficacious in preventing DHF among baseline seropositive individuals with or without Sri Lanka data included. Among baseline seronegative individuals there was a negative point estimate (~3%) of efficacy if Sri Lanka data were included, which changed to a positive point estimate (47.5%) when Sri Lanka data were excluded; nevertheless, the confidence intervals for both point estimates of efficacy were wide and spanned zero. In this baseline seronegative group, all cases of DHF in the vaccine group were DENV3, compared to one in the placebo group.

Table 4. Efficacy against severe dengue and dengue hemorrhagic fever (DHF) 57 months post dose 1 (exploratory analysis)

![Table 4](https://terrance.who.int/mediacentre/data/sage/SAGE_eYB_Sept2023.pdf)


The distribution by serotype is not specified in the analysis of seropositive cases.
Efficacy stratified by age group

Vaccine efficacy estimates in the safety set ~57 months after the first dose, stratified by age groups, are shown in Table 5.

Table 5. Vaccine efficacy in the safety set (~57 months), stratified by age group

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Placebo (n=6687)</th>
<th>TAK-003 (n=13,380)</th>
<th>VE (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4–5 years</td>
<td>VCD (per 100 person-years)</td>
<td>43.5 (25.3, 57.3)</td>
<td></td>
</tr>
<tr>
<td>Seropositive</td>
<td>59 (2.9)</td>
<td>59 (1.3)</td>
<td>54.1 (34.1, 68.0)</td>
</tr>
<tr>
<td>Seronegative</td>
<td>32 (2.1)</td>
<td>49 (1.6)</td>
<td>23.2 (–20.6, 50.8)</td>
</tr>
<tr>
<td>6–11 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seropositive</td>
<td>225 (2.0)</td>
<td>165 (0.7)</td>
<td>64.8 (57.0, 71.2)</td>
</tr>
<tr>
<td>Seronegative</td>
<td>96 (2.0)</td>
<td>79 (0.8)</td>
<td>60.5 (46.8, 70.7)</td>
</tr>
<tr>
<td>12–16 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seropositive</td>
<td>110 (1.4)</td>
<td>71 (0.4)</td>
<td>68.6 (57.7, 76.7)</td>
</tr>
<tr>
<td>Seronegative</td>
<td>25 (1.7)</td>
<td>19 (0.6)</td>
<td>63.6 (33.8, 79.9)</td>
</tr>
</tbody>
</table>

The point estimates for vaccine efficacy in children in the 4–5 years age group were lower compared to the other two age groups, especially in those who were baseline seronegative where it was not statistically significant. The lower efficacy estimates could partly be explained by the higher proportion of VCD cases due to DENV3 (against which the vaccine was less efficacious) in this age group.

Cumulative incidence stratified by serotype

The cumulative incidence of total VCD cases and hospitalized VCD cases by serotype is shown in Figures 8 and 9.

Figure 8. Cumulative incidence of virologically confirmed dengue (VCD) over 57 months after the first dose


There was a gradual accumulation of DENV1 VCD cases whereas there was a sharp increase in DENV2 cases in the early months, but there was a clear and early separation in the cumulative incidence curves between the vaccine and placebo groups for both serotypes.

For DENV3 there was a higher incidence of cases in the baseline seronegative individuals in the vaccine group, with separation in incidence between months 15 and 39 with no further separation thereafter. The case counts for DENV4 were low with no significant separation of incidence between the vaccine and control groups.
Figure 9. Cumulative incidence of hospitalized virologically confirmed dengue (VCD) over 57 months after the first dose


For hospitalized VCD cases, there was a clear separation of the incidence curves for DENV1 and DENV2 among both seropositive and seronegative individuals. For DENV3, among baseline seronegative individuals, the incidence curves were close together until month 18, after which the incidence in the vaccine group was higher than in the placebo group. This difference disappeared if the hospitalized cases from Sri Lanka were removed.

Data were presented on the clinical characteristics of hospitalized DENV3 cases among baseline seronegative subjects (Table 6). A higher proportion of cases with plasma leakage and thrombocytopenia was observed in the vaccine group compared to the control group, both when cases from Sri Lanka were included and excluded.
Table 6. Clinical characteristics of hospitalized DENV3 virologically confirmed dengue (VCD) among baseline seronegative subjects (post first dose to ~57 months)

<table>
<thead>
<tr>
<th></th>
<th>Placebo n=1812</th>
<th>TAK-003 n=3714</th>
<th>Placebo n=1564</th>
<th>TAK-003 n=3181</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of VCD cases</td>
<td>16</td>
<td>36</td>
<td>16</td>
<td>30</td>
</tr>
<tr>
<td>Number of hospitalized VCD cases (% of VCD)</td>
<td>3 (18.7%)</td>
<td>11 (30.6%)</td>
<td>3 (18.7%)</td>
<td>5 (16.7%)</td>
</tr>
<tr>
<td>Duration of febrile illness (days; median/mean; 95% CI)</td>
<td>10.0/10.0 (2.4, 22.4)</td>
<td>7.0/6.1 (6.7, 9.5)</td>
<td>10.0/10.0 (2.4, 22.4)</td>
<td>10.0/9.2 (6.5, 11.9)</td>
</tr>
<tr>
<td>Duration of fever (days; median/mean; 95% CI)</td>
<td>6.0/6.1 (2.5, 10.1)</td>
<td>6.0/5.5 (4.8, 6.2)</td>
<td>6.0/6.1 (2.5, 10.1)</td>
<td>5.0/5.0 (3.5, 8.5)</td>
</tr>
<tr>
<td>Duration of hospitalization (days; median/mean; 95% CI)</td>
<td>4.0/4.0 (1.5, 6.5)</td>
<td>7.0/6.6 (5.7, 7.6)</td>
<td>4.0/4.0 (1.5, 6.5)</td>
<td>7.0/6.6 (4.3, 8.9)</td>
</tr>
<tr>
<td>Evidence of bleeding, n/N (%)</td>
<td>2/3 (66.7)</td>
<td>3/11 (27.3)</td>
<td>2/3 (66.7)</td>
<td>2/5 (40.0)</td>
</tr>
<tr>
<td>Hematocrit increase ≥220%, n/N (%)</td>
<td>0/3</td>
<td>3/10 (30.0)</td>
<td>0/3</td>
<td>2/4 (50.0)</td>
</tr>
<tr>
<td>Platelet count ≤100x10^9/L, n/N (%)</td>
<td>1/3 (33.3)</td>
<td>7/11 (63.6)</td>
<td>1/3 (33.3)</td>
<td>3/5 (60.0)</td>
</tr>
<tr>
<td>Signs of circulatory failure, n/N (%)</td>
<td>0/3</td>
<td>3/10 (30.0)</td>
<td>0/3</td>
<td>2/4 (50.0)</td>
</tr>
<tr>
<td>ALT or AST &gt; 10 times upper limit of normal range, n/N (%)</td>
<td>0/3</td>
<td>0/10</td>
<td>0/3</td>
<td>0/4</td>
</tr>
<tr>
<td>Blood Transfusion and/or Replacement Therapy, n/N (%)</td>
<td>2/3 (66.7)</td>
<td>10/11 (90.9)</td>
<td>2/3 (66.7)</td>
<td>5/5 (100.0)</td>
</tr>
</tbody>
</table>

* refers to subjects in the event set, n/N refers to number of subjects/number of cases evaluated.
* Mean included in all figures except for Table 6.
GMT: geometric mean titer; virologically confirmed dengue.


Stratified analyses by year of follow-up
Vaccine efficacy point estimates against overall VCD declined from year 1 to 3 in baseline seropositive and seronegative subjects. For hospitalized VCD, there was no observed trend among baseline seropositive subjects (however, they have lower point estimates for years 2 and 3 compared to year 1). Among baseline seronegative subjects, vaccine efficacy declined after year 1.

Efficacy against asymptomatic infection
Takeda provided data from an exploratory analysis of the effect of TAK-003 on asymptomatic dengue infections conducted in the immunogenicity subset of the DEN-301 pivotal efficacy trial for whom serial blood samples were taken over time. Results show it can be assumed that the vaccine is unlikely to have any significant impact on disease transmission (3).

Immunogenicity in children
In baseline seropositive subjects, the geometric mean titers (GMTs) against all four DENV serotypes remained consistently above 100 up to 51 months after the first dose. In baseline seronegative subjects, GMTs also remained close to 100 during this period, although in this group the difference in titers against DENV2 and the other three serotypes was notable. GMTs were several-fold higher in the vaccine group than in the placebo group among baseline seronegative subjects.

Coadministration of TAK-003 with other vaccines
Two coadministration studies (DEN-305 and DEN-314) were conducted in nonendemic countries with yellow fever and hepatitis A vaccines to study the possible interactions of the TDV vaccine
with the most common vaccines used for travelers. In both studies the non-inferiority criteria were met.

Safety of the TAK-003 vaccine

Clinical data-safety of the TAK-003 vaccine in children and adults
The integrated safety analysis included data on solicited local adverse events within 7 days of vaccination, solicited systemic adverse events within 14 days of vaccination, and unsolicited adverse events within 28 days of vaccination among participants from ages 4 to 60 years. No alarm signals were detected.

Safety of TAK-003 in pregnant women
While animal studies do not indicate direct or indirect harmful effects of TAK-003 with respect to developmental and reproductive toxicity, the vaccine has not been studied in pregnant women during clinical development. There are limited data on pregnancy outcomes following inadvertent administration in women who were pregnant or who became pregnant shortly after vaccination.

As of 1 October 2020, 44 exposed pregnancies were identified (34 among TAK-003 recipients and 10 among placebo recipients). Most of the pregnancies resulted in live births (27 [79%] TAK-003 recipients and 5 [50%] placebo recipients). The frequency of spontaneous abortions for exposed versus nonexposed pregnancies was 4/34 (12%) versus 14/247 (6%) for TAK-003 exposed and 2/10 (20%) versus 5/114 (4%) in placebo exposed. These rates are well within the background rates for spontaneous abortions reported in the literature. One neonatal death occurred after an exposed pregnancy but was considered not to be causally related to TAK-003.

Since the available data are not sufficient to draw conclusions about the safety of TAK-003 during pregnancy, Takeda’s position remains that the vaccine is contraindicated during pregnancy and that women of childbearing potential should avoid pregnancy for at least one month following vaccination.

Evidence related to enhanced disease
As reported in the efficacy section, an excess of hospitalized dengue cases and a negative point estimate of vaccine efficacy were observed against DENV3 among baseline seronegative children and adolescents in the Phase 3 trial (see Table 3). However, the differences between the vaccine and placebo groups were not statistically significant. There was also a small excess in cases of severe dengue and DHF among baseline seronegative vaccinees (Table 6). All the severe cases among the seronegative vaccinees were caused by DENV3. While the differences were not statistically significant, given the history with Dengvaxia®, this raised potential safety concerns, but the trial data did not permit any firm conclusions.

Modeling the impact of TAK-003
Analysis was performed by researchers from Imperial College London. The impact of vaccination at the population and individual level was estimated, with the former calculated as the
proportion of cases averted in the entire population, and the latter calculated as the absolute number or proportion of cases averted in the first vaccinated cohort. Outcomes were calculated at 5, 10, and 20 years after the start of vaccination, with results at 10 years shown here.

The population-level impact of vaccination with TAK-003 was evaluated using a stochastic four-serotype dengue transmission model. The resulting VE against infection profiles show limited protection in seronegative recipients except for DENV2, and moderate but rapidly waning initial protection in seropositive recipients, against other serotypes except for DENV2, where protection is more sustained (although still partial). The impact of routine vaccination was simulated (varying vaccination coverage between 20% and 80% and the age of vaccination between 4 and 18 years) across nine transmission intensity settings expressed in terms of seroprevalence at 9 years of age (SP9) (from 10% to 90% in steps of 10%).

Figure 10 shows the population-level impact of vaccination (assuming the Brazilian demography) over 10 years. The impact was calculated as the proportion of cases averted in the entire population with results at 10 years. Positive impacts were seen against VCD and hospitalization over all ages of vaccination, with larger impacts in higher transmission settings and for increasing age at vaccination. Overall, the impact is modest, with an average proportion of cases averted not exceeding 15% and 20% for VCD and hospitalizations, respectively. Assuming moderate protection against infection (red curve) gives substantially higher population impacts than assuming no protection against infection (blue curve).

**Figure 10. Population-level impact of vaccination assuming Brazilian demography**

*Source:* WHO SAGE Background paper on dengue vaccines. Available from: [https://terrance.who.int/mediacentre/data/sage/SAGE_eYB_Sep2023.pdf](https://terrance.who.int/mediacentre/data/sage/SAGE_eYB_Sep2023.pdf)

*Note:* Cumulative proportion of hospitalizations (top row) and symptomatic cases (bottom row) averted by transmission setting (columns), expressed as the expected seroprevalence at 9 years old (SP9 = 20%, 40%, 60%, and 80%) by age of routine vaccination (horizontal axis) assuming 80% coverage over 10 years. Blue curves represent the impact assuming no VE against infection, and red curves assume a moderate impact against infection. Shaded regions represent 95% CI.
Figure 11 shows the individual-level impact of routine vaccination of 6-year-olds (using Brazilian demographics) in terms of the proportion of symptomatic disease and hospitalized cases averted in the first vaccinated cohort over 10 years. Results are shown for the whole cohort (left column) and stratified by serostatus (center and right columns). Both models show positive mean impacts (40–70% of hospitalizations averted), but the 95% uncertainty bounds include potentially negative impacts in seronegative recipients in low-mid transmission intensity settings (in baseline seronegative children only when the seroprevalence was 60% or higher in 9-year-olds, the lower bound of 95% range is above zero). Negative impacts are most likely for more pessimistic posterior estimates of VE for DENV3 and DENV4 and for simulations that generate extended periods of DENV3 and DENV4 incidence in the first 10 years after vaccination starts.

Figure 11. Individual-level impact of vaccination in terms of proportion of cases averted for Brazilian demography, 10 years post-vaccination


Note: The proportion of hospitalized and symptomatic cases averted (rows) in the first vaccinated cohort of 6-year-olds overall (all) and among baseline seropositive and seronegative vaccinees (columns) by transmission setting, expressed as the expected seroprevalence at 9 years old (horizontal axis) assuming a vaccination coverage of 80% using model (a) VI_D15 and (b) VS_D15. Solid line represents the mean, light shading represents overall uncertainty (95% CI), and dark shading represents uncertainty around the mean (95% CI).
Regulatory update

Market authorization summary
The vaccine was granted market authorization in Indonesia on 19 August 2022, in the European Union by the European Medicines Agency (EMA) on 5 December 2022, and in the United Kingdom on 26 January 2023 (4). Table 7 summarizes the marketing authorizations obtained to date. Applications for authorization are pending in other Wave 1 countries, and a Product Summary File has been submitted to WHO for prequalification. The expected timeframe to receive WHO prequalification is between September 2023 and February 2024.

Table 7. Regulatory status information from the manufacturer as of October 2023

<table>
<thead>
<tr>
<th>Country</th>
<th>Date of the latest market authorization granted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indonesia</td>
<td>August 2022</td>
</tr>
<tr>
<td>European Union (27 member states),</td>
<td>December 2022</td>
</tr>
<tr>
<td>Liechtenstein, Northern Ireland</td>
<td></td>
</tr>
<tr>
<td>Norway</td>
<td>December 2022</td>
</tr>
<tr>
<td>Iceland</td>
<td>December 2022</td>
</tr>
<tr>
<td>Great Britain</td>
<td>January 2023</td>
</tr>
<tr>
<td>Brazil</td>
<td>March 2023</td>
</tr>
<tr>
<td>Argentina</td>
<td>April 2023</td>
</tr>
<tr>
<td>Thailand</td>
<td>May 2023</td>
</tr>
</tbody>
</table>

Age indication and administration guidelines
EMA has authorized the use of the vaccine for individuals aged 4 years and above, without an upper age limit. This decision was made despite the lack of data for subjects over 60 years of age, based on the potential benefits of vaccination for seropositive individuals in this age group. Older adults face a higher risk of severe dengue, DHF, or dengue shock syndrome (DSS) and are more likely to require hospitalization. The vaccine is administered in two subcutaneous injections of 0.5 mL each, spaced three months apart. It is contraindicated in pregnant or breastfeeding women, as well as in individuals with weakened immune systems due to diseases, immune-affecting medications, or HIV infection.

Pharmaceutical presentation and handling
The pharmaceutical form is a powder and diluent for injection solution. It comes in lyophilized single-dose vials with 0.22% sodium chloride as the diluent. Each secondary package contains 10 single-dose lyophilized vials and 10 diluent vials.

The vaccine, branded as Qdenga®, should be administered immediately after reconstitution. Its chemical and physical stability post-reconstitution lasts for two hours at room temperature (up to 32.5 °C). After this period, the vaccine should be discarded and must not be refrigerated again. From a microbiological standpoint, Qdenga® is recommended for immediate use. Any in-use storage times and conditions beyond immediate use are the responsibility of the user.
Withdrawal of applications in the United States of America and Singapore

Takeda has withdrawn its biologics license application (BLA) to the US FDA. The manufacturer issued a statement regarding its voluntary withdrawal of the BLA following discussions on aspects of data collection, which cannot be addressed within the current BLA review cycle (5).

Takeda’s planned post-licensure activities to assess safety and effectiveness

The safety specifications submitted as part of the risk management plan to EMA included no important identified risks. Important potential risks included: anaphylaxis, including anaphylactic shock; dengue disease due to waning immunity over time; and severe and/or hospitalized dengue caused by DENV3 or DENV4 in vaccinated individuals who had not been previously infected by the dengue virus. Missing safety information included: safety in pregnant and lactating women; safety and immunogenicity in immunocompromised persons; safety and immunogenicity of concomitant administration with hepatitis A and yellow fever vaccines; and safety and reactogenicity of a booster dose. The routine pharmacovigilance plan will aim to collect data on the above safety specifications.

The planned post-authorization studies include studies on (i) long-term safety and efficacy (DEN-301); (ii) long-term safety and antibody persistence (DEN-303); and (iii) immunogenicity and safety of coadministration with human papillomavirus (HPV) vaccine (DEN-308). In addition, a post-authorization effectiveness study (DEN-401) is planned to assess the impact of TAK-003 against hospitalized dengue. The planned trial size and location will be determined to overcome limitations in the pivotal study to assess the impact on severe/hospitalized cases due to DENV3 and DENV4. The current study design is a multi-country, multi-site nested case-control study in a cohort of 70,000 participants for whom the baseline serostatus will be determined. The study will be conducted in Southeast Asia in areas known to have circulation of DENV3 and DENV4. The planned study duration is at least 36 months. Based on the number of cases observed in the placebo arm of the pivotal trials of Dengvaxia® and TAK-003, the study is estimated to accrue approximately 36 hospitalized cases of DENV3 and 25 hospitalized cases of DENV4 in seronegative subjects. Controls will be individuals, matched for age and area of residence, who are not hospitalized for VCD.
Question for the TAG:
- Should vaccination with RSVpreF vaccine be recommended for pregnant people to prevent RSV disease in infants?

Global burden of disease
Across the world, respiratory syncytial virus (RSV) is considered the most common cause of infant pneumonia and bronchiolitis and the leading cause of pediatric hospitalizations and pneumonia deaths in the first six months of life. Every year, it is estimated that RSV is responsible for 33 million episodes of acute lower respiratory tract disease (LRTD), approximately 3.6 million hospitalizations, and over 100,000 deaths among children younger than 5 years worldwide. Children younger than 6 months account for 20% of acute RSV LRTD episodes and almost half (45%) of all RSV deaths in children younger than 5 years (Figure 12). More than 97% of RSV-related deaths across all age groups are in lower-middle-income countries (LMIC). Overall, 67% of deaths occur in the community before any health care is sought (6).

Figure 12. Global estimates of RSV cases, hospitalizations, and deaths in children <5 years old


Burden of disease in the Americas
RSV poses a substantial burden in the Americas, affecting individuals of all ages, and contributes substantially to morbidity and mortality. While there is a need to better estimate the actual burden of disease associated with RSV in the vulnerable population in the Region, historical integration of RSV testing into the influenza and other respiratory virus surveillance systems provides epidemiological data as a tool to inform vaccine introductions based on the relative proportion of RSV in respiratory hospitalizations and ambulatory cases.

Data reported from Member States in the Americas to the PAHO integrated respiratory surveillance network SARI Plus indicate that RSV contributes significantly to the burden of respiratory diseases in the Region, with a high number of RSV-associated hospitalizations (Figure 13). By age group, RSV-associated cases and hospitalizations have been primarily reported among children, especially in infants younger than 2 years (Figure 14) (7, 8). The available figures may be underestimated because testing of medically attended RSV-associated disease is not systematically conducted.
Figure 13. Number of severe acute respiratory infections (SARI) cases by etiological agent, reported to FluID from January 2022 to November 2023, Region of the Americas


Figure 14. RSV-positive influenza-like illness (ILI) and severe acute respiratory infections (SARI) cases by age groups, reported to FluID in 2023, Region of the Americas

Source: PAHO/WHO FluID and FluNet Platforms.

In a study conducted in 2022, national incidence rates and the number of episodes associated with RSV in children ages 0–5 years were estimated for 26 countries in the Americas (6). In those countries, estimated incidence rate ranged from 46.0 to 52.3 RSV-associated episodes per 1000 children per year. Higher annual burden was observed in Brazil with 717 437 RSV-associated episodes, Mexico with 530 334, Colombia with 181 578, and Argentina with 177 889 RSV-associated episodes per year (Supplementary Table 1).

Seasonality
RSV in the Americas exhibits distinct seasonality patterns based on geographic location, altitude, and climate factors. In temperate regions, RSV peaks during winter months, showing a temperature-dependent pattern. In the Southern Hemisphere temperate countries, the season usually begins in April, peaks in July, and ends in October. In the Northern Hemisphere countries, the season usually begins in October, peaks in January, and ends in April. Both hemispheres generally experience 5–6 months of RSV activity. In tropical areas, higher RSV activity is observed during the rainy season, with no clear seasonal pattern (Figure 15) (8, 9).
Mode of transmission, people at risk, and clinical presentation

Transmission occurs through droplet spread (sneezing or coughing) and transference from contaminated surfaces by respiratory discharges of an infected person.

People at risk for severe RSV disease include infants younger than 6 months, premature infants, and children with chronic lung disease, Down syndrome, and congenital heart disease. Also, immunocompromised children younger than 18 years are at risk of severe disease (10). Risk factors for death include factors related to poor access to care, cost of care, and limited number of beds (in the intensive care unit [ICU] and/or in the emergency department) during an RSV epidemic (6).

In the United States of America, most infants (68%) are infected in the first year of life and 97% by the end of the first 24 months of life (11). Repeated infections occur over the lifespan. In infants, RSV disease can range from mild, flu-like disease to bronchiolitis, pneumonia, and death. In older children and adults without comorbidities, repeated upper respiratory tract infections are common and range from subclinical infection to symptomatic upper respiratory tract disease. Most hospitalization due to RSV occurs in the first 2–3 months after birth. The highest proportion of hospitalized cases in infants younger than 2 years had no underlying medical conditions (12, 13).
In addition to the pediatric burden of disease, RSV is increasingly being recognized as an important pathogen in older adults, with infection leading to an increase in hospitalization rates among those aged 65 years or older and to increased mortality rates among the frail elderly, which approach the rates seen for influenza.

**Regional diagnostic capacity and surveillance networks**
In the Region of the Americas, countries conduct surveillance for influenza and other respiratory viruses, including RSV, through the National Influenza Centers and National Reference Laboratories as part of the WHO Global Influenza Surveillance and Response System (GISRS) and the PAHO Severe Acute Respiratory Infections network (SARInet Plus) (7, 14). Most PAHO Member States and territories have molecular platforms, with real-time equipment for molecular detection of influenza and other respiratory viruses (ORV) detection, including RSV (Figure 16). In addition, most countries in the Region have next-generation sequencing platform and genomic surveillance capacity implemented. In countries where sequencing is not available, samples are shipped for external sequencing at one of the eight regional sequencing laboratories of the network (15). Repository viruses from molecular diagnostic and genomic surveillance are reported in a timely fashion to PAHO and WHO through the FluNet platform for monitoring respiratory virus trends as well as for identifying any unusual or emerging respiratory virus.

**Figure 16. Laboratory capacity for virological surveillance of respiratory viruses in the Region of the Americas**

![Image](image.png)

*Source: PAHO and Member States reports.*

**Treatment and prevention of RSV disease in infants**

**Case management**
Current treatment measures are limited to supportive care. Hospitalization is recommended for patients with severe symptoms or at risk of severe symptoms, those who require supplemental fluids, and those who require respiratory support. The mean length of stay in hospital for children...
with severe pneumonia was estimated at 5.8 days (interquartile range [IQR] 5.3–6.4) in LMIC and 7.7 days (IQR 5.5–9.9) in high-income countries (HIC) (16).

**Monoclonal antibodies**

Monoclonal antibodies (mAb) prevent severe disease caused by RSV in newborns and infants at high risk for RSV. Palivizumab is a short-lasting mAb for the prevention of severe RSV in high-risk infants and requires monthly doses during the RSV season (5–6 doses). It was approved in 1999 and remained the only prophylaxis option until 2023.

Nirsevimab (Beyfortus, Sanofi, and AstraZeneca) is a long-acting one-dose mAb that protects against RSV disease for at least five months and is indicated for newborns entering their first RSV season. It can be used in infants up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season. It has been approved for use in the European Union (October 2022) and in the United States (July 2023) (17, 18). Top-line results from the Phase 3 MELODY trial estimated that efficacy of Nirsevimab against medically attended RSV-associated LRTD, medically attended RSV-associated LRTD with hospitalization, and very severe medically attended RSV-associated LRTD through 150 days post dose was 76.4% (95% CI [62.3, 85.2]), 76.8% (95% CI [49.4, 89.4]), and 78.6% (95% CI [48.8, 91.0]), respectively (19).

Nirsevimab is given as single dose of 50 mg for newborns <5 kg, 100 mg for newborns ≥5 kg and 200 mg for high-risk infants entering their second RSV season. In the United States, the public sector price is USD 395 per 50 mg or 100 mg dose. The private-sector price for Nirsevimab is USD 495 per dose for 50 mg and 100 mg doses and USD 990 per dose for a 200 mg dose (two 100 mg doses) (20).

**Vaccination in pregnant women**

Transplacental transfer of vaccine-induced maternal antibodies can protect infants from birth up to 6 months. An RSV prefusion F protein (RSVpreF) vaccine for use in pregnant individuals to prevent LRTD caused by RSV in infants younger than 6 months has recently received market authorization. It contains two recombinant stabilized RSV prefusion F antigens representing subgroups RSV-A and RSV-B. Prefusion F protein is the primary target of neutralizing antibodies that block RSV infection. Abrysvo® (Pfizer Inc.) is currently the only vaccine available for use in pregnant individuals and was approved by the U.S. Food and Drug Administration (FDA) and by the European Medicines Agency (EMA) in August 2023 (21, 22). See Table 8 for additional information. Other maternal RSV vaccines and monoclonal antibodies to prevent RSV disease are under investigation (23).

**Table 8. Bivalent RSV prefusion F (RSVpreF) maternal vaccine (Abrysvo, Pfizer Inc.)**

<table>
<thead>
<tr>
<th>Indications and usage</th>
<th>Active immunization of pregnant individuals for the prevention of lower respiratory tract disease (LRTD) and severe LRTD caused by</th>
</tr>
</thead>
</table>

3 Very severe was defined as medically attended RSV LRTI with hospitalization and requirement for supplemental oxygen or intravenous fluids.
<table>
<thead>
<tr>
<th><strong>Composition</strong></th>
<th>Powder and solvent for solution for injection. After reconstitution, one dose (0.5 mL) contains two RSV prefusion F antigens representing subgroups RSV-A and RSV-B (60 µg for each antigen).</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Administration</strong></td>
<td>Intramuscular injection into the deltoid region of the upper arm.</td>
</tr>
<tr>
<td><strong>Mechanism of action</strong></td>
<td>Following intramuscular administration, the prefusion F antigens elicit an immune response. In infants born to mothers who were vaccinated with RSVpreF vaccine, protection against RSV-associated LRTD is due to transplacental transfer of RSV neutralizing antibodies.</td>
</tr>
<tr>
<td><strong>Storage and handling requirement</strong></td>
<td>Supplied as pre-filled single 0.5 mL dose, or as a 5-pack or 10-pack of single-dose kits. Reconstitution required: single dose vial of lyophilized powder, reconstitution supplies included in kit. Product should be refrigerated (2–8 °C) in original container, protected from light. After reconstitution, the product should be administered within 4 hours.</td>
</tr>
<tr>
<td><strong>Cost per dose</strong></td>
<td>Price in the United States market (November 2023): USD 295 per dose.</td>
</tr>
<tr>
<td><strong>WHO prequalification</strong></td>
<td>Expected in 2024.</td>
</tr>
</tbody>
</table>

**Vaccine efficacy and safety**

Evidence of efficacy and safety were derived from multi-country trials that randomized pregnant persons to receive maternal RSVpreF vaccination or placebo during 24–36 weeks of gestation.

The Phase 2b trial was conducted in five countries\(^4\) to evaluate the safety, tolerability, and immunogenicity of the RSV vaccine in pregnant women (24). The Phase 3 trial MATISSE (Maternal Immunization Study for Safety and Efficacy) is a multicenter, randomized (1:1), double-blind, placebo-controlled study conducted in 18 countries\(^5\) over four RSV seasons (two seasons in the Northern Hemisphere and two seasons in the Southern Hemisphere from 2020 to 2022). This clinical trial evaluated the efficacy and safety of maternal RSVpreF immunization against medically attended RSV-associated LRTD in infants born to pregnant individuals vaccinated between weeks 24 and 36 of gestation. In this study, 3695 pregnant individuals with

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\(^4\) Argentina, Chile, New Zealand, South Africa, and United States.

\(^5\) Argentina, Australia, Brazil, Canada, Chile, Denmark, Finland, Gambia, Japan, Mexico, Netherlands, New Zealand, Philippines, Republic of Korea, South Africa, Spain, Taiwan, and United States of America.
uncomplicated, singleton pregnancies were randomized to the Abrysvo RSVpreF vaccine group and 3697 to placebo (25).

**Vaccine efficacy**

Vaccine administered during pregnancy was effective against medically attended severe RSV-associated LRTD in infants. Vaccine efficacy (VE) against severe LTRD caused by RSV in infants was 81.8% and 69.4% at 90 days and 180 days, respectively. The VE against all medically attended LTRD was 57.1% and 51.3% at 90 days and 180 days, respectively. See Table 9 and 10 for details.

**Table 9. Vaccine efficacy of RSVpreF vaccine (Abrysvo®) against severe medically attended lower respiratory tract disease (LRTD)† caused by RSV in infants from birth through 6 months of age by active immunization of pregnant individuals**

<table>
<thead>
<tr>
<th>Time period</th>
<th>RSVpreF vaccine Number of cases N = 3495</th>
<th>Placebo Number of cases N = 3480</th>
<th>VE % (CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>90 days</td>
<td>6</td>
<td>33</td>
<td>81.8 (40.6, 96.3)</td>
</tr>
<tr>
<td>120 days</td>
<td>12</td>
<td>46</td>
<td>73.9 (45.6, 88.8)</td>
</tr>
<tr>
<td>150 days</td>
<td>16</td>
<td>55</td>
<td>70.9 (44.5, 85.9)</td>
</tr>
<tr>
<td>180 days</td>
<td>19</td>
<td>62</td>
<td>69.4 (44.3, 84.1)</td>
</tr>
</tbody>
</table>

*Notes: †Severe medically attended LRTD: a patient with an RT-PCR confirmed RSV illness with at least one of the following: tachypnea (respiratory rate ≥70 breaths per minute [<2 months of age], ≥60 breaths per minute [≥2 to 12 months of age], or ≥50 breaths per minute [≥12 to 24 months of age]); SpO2 measured in room air <93%; high-flow nasal cannula or mechanical ventilation (invasive or noninvasive), ICU admission for >4 hours and/or failure to respond/unconscious. *VE: vaccine efficacy. CI: confidence interval (99.5% at 90 days, 97.58% at later intervals).*

**Table 10. Vaccine efficacy of RSVpreF vaccine (Abrysvo®) against all medically attended lower respiratory tract disease (LRTD)† caused by RSV in infants from birth through 6 months of age by active immunization of pregnant individuals**

<table>
<thead>
<tr>
<th>Time period</th>
<th>RSVpreF vaccine Number of cases N = 3495</th>
<th>Placebo Number of cases N = 3480</th>
<th>VE % (CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>90 days</td>
<td>24</td>
<td>56</td>
<td>57.1 (14.7, 79.8)</td>
</tr>
<tr>
<td>120 days</td>
<td>35</td>
<td>81</td>
<td>56.8 (31.2, 73.5)</td>
</tr>
<tr>
<td>150 days</td>
<td>47</td>
<td>99</td>
<td>52.5 (28.7, 68.9)</td>
</tr>
<tr>
<td>180 days</td>
<td>57</td>
<td>117</td>
<td>51.3 (29.4, 66.8)</td>
</tr>
</tbody>
</table>

*Notes: †Medically attended LRTD: a patient with an RT-PCR confirmed RSV illness with one or more of the following respiratory symptoms: tachypnea (respiratory rate ≥60 breaths per minute [<2 months of age], ≥50 breaths per minute [≥2 to 12 months of age], or ≥40 breaths per minute [≥12 to 24 months of age]); SpO2 measured in room air <95%; chest wall indrawing. *VE: vaccine efficacy. CI: confidence interval (99.5% at 90 days, 97.58% at later intervals).*

Also, the study assessed the VE within 360 days after birth. VE for RSV medically attended LRTD within 210 to 360 days after birth varied from 44.9% to 41.0% for 210 days and 360 days after birth, respectively. The VE against hospitalization caused by RSV within 360 days after birth was 33.3% (−16.6%, 62.9%), the wide confidence intervals resulting from the small number of
hospitalized children in the trial. VE against LTRD caused by RSV occurring within 180 days was higher for women vaccinated later in pregnancy (30 to 36 weeks of gestation) compared to women vaccinated early in pregnancy (between 24 and 29 weeks), although confidence intervals were overlapping. See Table 11 for details.

Table 11. Vaccine efficacy by maternal gestation age for medically attended lower respiratory tract disease (LRTD) and severe LRTD occurring within 180 days

<table>
<thead>
<tr>
<th></th>
<th>Gestational age</th>
<th>Vaccine efficacy % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medically attended</td>
<td>24–29 weeks</td>
<td>30.9% (−14.4, 58.9)</td>
</tr>
<tr>
<td>LRTD</td>
<td>30–36 weeks</td>
<td>62.4% (41.6, 76.4)</td>
</tr>
<tr>
<td>Severe LRTD</td>
<td>24–29 weeks</td>
<td>57.2% (10.4, 80.9)</td>
</tr>
<tr>
<td></td>
<td>30–36 weeks</td>
<td>78.1% (52.1, 91.2)</td>
</tr>
</tbody>
</table>

The MATISSE study was not powered to assess vaccine efficacy against deaths averted in infants. Only one death was reported in the control group and zero deaths in the vaccine group.

The RSVpreF vaccine (Abrysvo, Pfizer Inc.) has not been studied in pregnant individuals at less than 24 weeks of gestation. The efficacy and safety of the vaccine have not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. However, it is expected that the efficacy of the vaccine may be lower in immunosuppressed individuals. The trial did not assess the vaccine efficacy and safety to support the vaccination with additional doses in subsequent pregnancies.

Vaccine safety

No statistically significant difference in neonatal deaths was observed between intervention and control groups, although the number of deaths was lower in the vaccinated group compared with the control group: 5 (0.1%) in the RSVpreF group versus 12 (0.3%) in the control group.

Safety data from the Pfizer clinical trial showed a numerical excess of preterm births (<37 weeks) in the vaccinated group (5.7%, or 202 out of 3568 infants), although this difference was not statistically significantly different from the placebo group (4.7%, or 169 out of 3558 infants). Most infants born preterm in the vaccine group were late preterm births born at a gestational age of 36 weeks (72%, or 49 out of 68). Even in those mothers vaccinated at 24–28 weeks of gestational age, most preterm births were still late preterm, with birth occurring at 35–36 weeks. Moreover, most preterm births (60.2%) occurred 30 or more days after vaccination. In the trial, an excess of preterm births in the vaccinated group was observed in the upper middle-income countries (UMIC) of Argentina and South Africa, but no excess was observed in high-income countries (HIC), even though gestational age at vaccination was similar between the HIC and UMIC. Available data were insufficient to establish or exclude a causal relationship between preterm birth and RSVpreF vaccine.
More cases of hypertensive disorders of pregnancy (including preeclampsia) were observed among RSVpreF vaccine recipients (1.8%; 95% CI [1.4, 2.3]) compared with placebo recipients (1.4%; 95% CI [1.1, 1.9]), although the differences were not statistically significant. No cases of Guillain-Barré syndrome or other inflammatory neurologic events were reported in the Phase 2b or Phase 3 trials among pregnant persons.

According to the manufacturer, RSVpreF should not be administered to a person with a history of severe allergic reaction, such as anaphylaxis, to any component of this vaccine. Adults with a minor acute illness, such as a cold, can receive RSV vaccination. Moderate or severe acute illness, with or without fever, is a precaution to vaccination. Vaccination should generally be deferred until the patient improves.

In pregnant individuals, the most common side effects (≥10%) included pain at the injection site, headache, muscle pain, and nausea. Infants born to pregnant individuals experienced low birthweight below 2.5 kg (5.1%; 95% CI [4.4%, 5.8%] in the RSVpreF vaccine group versus 4.4%; 95% CI [3.7%, 5.1%] in the placebo group) and neonatal jaundice (7.2%; 95% CI [6.4%, 8.1%] in the RSVpreF vaccine group versus 6.7%; 95% CI [5.9%, 7.6%] in the placebo group).

Women with high-risk pregnancies such as those with a current risk of preterm birth, multiple pregnancy, or a previous infant with a clinically significant congenital anomaly were excluded from the clinical trials. Therefore, there is no information available for these groups.

Regarding simultaneous administration with other vaccines, in a Phase 2b study, RSVpreF was safe and well tolerated when administered with tetanus, diphtheria, and pertussis vaccine (Tdap) or alone in nonpregnant women 18–49 years of age. Immune responses induced by Tdap administered with RSVpreF were noninferior for the tetanus and diphtheria components of Tdap, but not for pertussis (26). In accordance with the U.S. Centers for Disease Control and Prevention (CDC) General Best Practices Guidelines for Immunization, maternal RSVpreF vaccine can be administered to pregnant persons with other recommended vaccines, such as Tdap, influenza, and COVID-19 vaccines, without regard to timing, including simultaneous vaccination at different anatomic sites on the same day (27).

**Vaccine effectiveness and impact**
Currently, there are no data available on vaccine effectiveness and impact assessment since the vaccine has been recently approved in the United States and Europe. Several post-authorization observational studies are ongoing in the United States with expected first results in 2024. VISION, the multi-state electronic health record network in the United States, will be powered to evaluate vaccine effectiveness against hospitalizations at around 25% vaccine coverage. Also, the New Vaccine Surveillance Network (NVSN), an active prospective population-based surveillance network for pediatric viral infections, will produce vaccine effectiveness estimates once sufficient data points have been accrued. In Latin America, the REVELAC-i network could also be adapted to monitor and evaluate the vaccine effectiveness of the maternal RSVpreF vaccine in preventing hospitalization in infants (28).
The WHO Strategic Advisory Group of Experts on Immunization (SAGE) has requested that an impact study be conducted to evaluate the full public health value and safety of the RSV vaccine to support country decision-making. This impact study is a randomized trial that will be conducted in LMIC in 2024 (29).

**Modeling studies**

**Cost-effectiveness**

A systematic literature review estimated the RSV treatment costs for infants in the United States at USD 709.6 million annually, representing USD 187 per overall birth and USD 227 per publicly funded birth. The mean RSV medical costs in children younger than 5 years was estimated at USD 12 315 (USD 11 905–12 725) per the entire duration of hospital stay, USD 501 (USD 484–517) per emergency department visit, and USD 73 (USD 41–105) per ambulatory visit (30). Cost-effectiveness may differ across countries based on the cost of the vaccine, medical costs, burden of disease, coverage, etc.

A model based on the United States showed that RSVpreF has the potential to be cost-effective versus no intervention (natural history) (31). The model assumed a base case of 3.7 million births with a 50% coverage in the first RSV season, preventing only LTRD and a cost per dose of USD 295. The estimated total cost of the intervention was USD 2.1 billion versus USD 1.6 billion for no intervention. The incremental cost-effectiveness ratio (ICER) for RSVpreF vaccine was USD 400 304 per quality-adjusted life year (QALY) saved when assuming year-round administration, and USD 167 289/QALY saved when administered seasonally (September–January) in the continental United States based on a pre-pandemic typical RSV season.

**Impact evaluations**

A model assuming 60% vaccine efficacy in 73 LMIC estimated that vaccination of pregnant women could avert between 10.1 million and 12.5 million cases, 2.8 million to 4.0 million hospitalizations, 123.7 thousand to 177.7 thousand deaths, and 8.5 to 11.9 disability-adjusted life years (DALY) projected over two years (32). Another model assumed 50% vaccination coverage and estimated that 1100 doses administered to pregnant women would avoid one ICU case, 242 doses would prevent one inpatient, 115 doses would prevent one emergency department visit, and 40 doses would prevent one outpatient care. This model was not powered to estimate deaths averted (15).

**Vaccine access for the Region of the Americas**

As the Region’s prominent solidarity platform for access to vaccines, PAHO Revolving Fund (RF) has been closely following the developments for RSV vaccine pipeline with regular consultations with suppliers. At this stage, the RF does not foresee any supply capacity constraints for accessing RSV vaccine. Based on the TAG recommendation, and considerations of use by countries, an estimated demand can be established as a basis for inclusion of this vaccine in the RF.

**Awareness and acceptance of RSV vaccine during pregnancy**
A recent survey conducted in the United States between December 2022 and January 2023 showed that of the 523 participants recruited (pregnant and recently pregnant people), 61% responded that they definitely or probably would get the RSV vaccine while pregnant. Among those who did not indicate they definitely would get the vaccine, the most common reason, indicated by 45% of women, was safety concerns. Other common concerns, indicated by 20% or greater of respondents, included lack of RSV knowledge and concerns about vaccination causing or intensifying RSV infection.

A qualitative study conducted in Kenya found that pregnant women’s concerns about a potential RSV vaccine include vaccine side effects and effect on fetus and baby after birth including positive benefits, and that pregnant women were familiar with RSV symptoms in babies but were unaware of the name of the disease or its mode of transmission. The overarching concern of pregnant women was vaccine safety (33).

Primary determinants for vaccine demand identified in a study conducted among pregnant women in Jordan include knowledge, attitude, and beliefs about RSV and its vaccination; perceived risks and concerns related to the vaccine and the disease in infants; convenient access to vaccination and its prompt availability; social influence and support; personal experience of vaccination; the belief in vaccine conspiracy; and the calculation of decision-making to get vaccinated. Vaccine acceptance was 70% among women of childbearing age in the study (34).

Conclusions

- LTRD caused by RSV is considered a major public health problem with high burden of disease, especially in infants younger than 6 months and particularly in low- and middle-income countries.
- RSVpreF vaccine (Abrysvo, Pfizer Inc.) is the only vaccine currently available indicated for active immunization of pregnant individuals to prevent RSV-associated LRTD in infants born to pregnant individuals vaccinated between weeks 24 and 36 of gestation. (35)
- Based on the clinical trials, RSVpreF vaccine (Abrysvo, Pfizer Inc.) has shown to be effective at preventing LRTD and severe LRTD caused by RSV in infants from birth through 6 months of age. (36)
- The majority of side effects with RSVpreF vaccine were mild or moderate.
- An excess of preterm births and hypertension complications have been observed in the vaccinated group versus placebo, although differences were not statistically significant. The imbalance of preterm birth was higher in UMIC. Reasons for the imbalance remain unclear.
- The RSVpreF vaccine (Abrysvo, Pfizer Inc.) could be included in the PAHO Revolving Fund, subject to technical and contractual aspects. The supplier has indicated that there are no supply constraints. WHO prequalification is expected in 2024.
- Models in the United States indicate that an immunization program with RSVpreF vaccine in pregnant individuals to protect infants younger than 6 months could be cost-effective versus no intervention. Seasonal vaccination was demonstrated to be more cost-effective than year-round vaccination.
• Use of monoclonal antibodies (e.g., Nirsevimab) can be considered in conjunction with the vaccine to prevent RSV-associated disease in newborns. See Supplementary Table 2 for advantages and disadvantages/challenges of RSVpreF vaccine and Nirsevimab.

• To date, there are no data available from studies on the effectiveness or impact of this vaccine on deaths averted among infants. There are a few post-authorization studies and models ongoing to estimate vaccine effectiveness, impact, and safety of the vaccine.
Supplementary Table 1. Estimated incidence rate and number of episodes of RSV-associated lower tract respiratory infections in children aged 0 to <5 years in the Region of the Americas

<table>
<thead>
<tr>
<th>Subregion</th>
<th>Country</th>
<th>Incidence rate, per 1 000 children per year (uncertainty range)</th>
<th>Number of episodes (uncertainty range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>North America</td>
<td>Mexico</td>
<td>48.0 (35.4–65.1)</td>
<td>530 334 (391 316–718 739)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central America</td>
<td>Costa Rica</td>
<td>47.6 (35.1–64.5)</td>
<td>16 705 (12 326–22 640)</td>
</tr>
<tr>
<td></td>
<td>El Salvador</td>
<td>48.1 (35.5–65.2)</td>
<td>27 741 (20 470–37 597)</td>
</tr>
<tr>
<td></td>
<td>Guatemala</td>
<td>50.9 (37.6–69.0)</td>
<td>104 737 (77 282–141 946)</td>
</tr>
<tr>
<td></td>
<td>Honduras</td>
<td>49.7 (36.7–67.4)</td>
<td>50 267 (37 090–68 125)</td>
</tr>
<tr>
<td></td>
<td>Nicaragua</td>
<td>52.3 (38.6–70.9)</td>
<td>34 618 (25 543–46 916)</td>
</tr>
<tr>
<td></td>
<td>Panama</td>
<td>52.2 (38.5–70.7)</td>
<td>20 293 (14 974–27 503)</td>
</tr>
<tr>
<td>Caribbean</td>
<td>Cuba</td>
<td>46.0 (34.0–62.4)</td>
<td>27 012 (19 932–36 609)</td>
</tr>
<tr>
<td></td>
<td>Dominican Republic</td>
<td>48.2 (35.5–65.3)</td>
<td>48 488 (35 778–65 714)</td>
</tr>
<tr>
<td></td>
<td>Guyana</td>
<td>50.0 (36.9–67.8)</td>
<td>3 751 (2 768–5 083)</td>
</tr>
<tr>
<td></td>
<td>Haiti</td>
<td>50.9 (37.6–69.0)</td>
<td>64 393 (47 514–87 269)</td>
</tr>
<tr>
<td></td>
<td>Jamaica</td>
<td>49.8 (36.8–67.5)</td>
<td>11 607 (8 564–15 730)</td>
</tr>
<tr>
<td></td>
<td>Saint Lucia</td>
<td>50.4 (37.2–68.2)</td>
<td>504 (372–682)</td>
</tr>
<tr>
<td></td>
<td>Saint Vincent and the Grenadines</td>
<td>48.7 (35.9–65.9)</td>
<td>438 (323–593)</td>
</tr>
<tr>
<td></td>
<td>Suriname</td>
<td>51.0 (37.6–69.1)</td>
<td>2 701 (1 993–3 661)</td>
</tr>
<tr>
<td></td>
<td>Trinidad and Tobago</td>
<td>50.3 (37.1–68.2)</td>
<td>4 577 (3 377–6 203)</td>
</tr>
<tr>
<td>Andean</td>
<td>Bolivia (Plurinational State of)</td>
<td>48.5 (35.8–65.7)</td>
<td>57 480 (42 412–77 900)</td>
</tr>
<tr>
<td></td>
<td>Colombia</td>
<td>48.7 (35.9–66.0)</td>
<td>181 578 (133 981–246 085)</td>
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<tr>
<td></td>
<td>Ecuador</td>
<td>48.9 (36.1–66.3)</td>
<td>81 335 (60 014–110 229)</td>
</tr>
<tr>
<td></td>
<td>Peru</td>
<td>47.8 (35.3–64.8)</td>
<td>134 393 (99 164–182 137)</td>
</tr>
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<td></td>
<td>Venezuela (Bolivarian Republic of)</td>
<td>50.4 (37.2–68.3)</td>
<td>121 936 (89 973–165 254)</td>
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<tr>
<td>Southern Cone</td>
<td>Argentina</td>
<td>47.5 (35.1–64.4)</td>
<td>177 889 (131 258–241 085)</td>
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<tr>
<td></td>
<td>Brazil</td>
<td>49.2 (36.3–66.7)</td>
<td>717 437 (529 373–972 311)</td>
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<tr>
<td></td>
<td>Chile</td>
<td>47.7 (35.2–64.7)</td>
<td>56 448 (41 651–76 501)</td>
</tr>
<tr>
<td></td>
<td>Paraguay</td>
<td>51.1 (37.7–69.2)</td>
<td>35 701 (26 343–48 384)</td>
</tr>
<tr>
<td></td>
<td>Uruguay</td>
<td>48.5 (35.8–65.8)</td>
<td>11 554 (8 525–15 658)</td>
</tr>
</tbody>
</table>

**Supplementary Table 2. Advantages and disadvantages of maternal RSVpreF vaccination and Nirsevimab administration to infants to prevent respiratory syncytial virus (RSV) lower respiratory tract infection in infants**

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<thead>
<tr>
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<th>Advantages</th>
<th>Disadvantages/challenges</th>
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| **RSVpreF vaccine** | Provides protection immediately after birth.  
Experience delivering vaccines to pregnant individuals against diseases like influenza, tetanus, and COVID-19.  
Feasible in the community and rural areas.  
Can benefit and improve antenatal care, encouraging pregnant patients to attend more well-care visits. | Protection potentially reduced if less antibodies are produced or are transferred from pregnant person to baby (e.g., pregnant person is immunocompromised, or infant born soon after vaccination).  
Narrow gestational age window for vaccination of pregnant women.  
Programmatic challenges.  
Children delivered prematurely (those at greater risk for RSV) will not be protected (born to unvaccinated mother).  
| **Nirsevimab** | Assures direct receipt of antibodies rather than relying on transplacental transfer.  
No potential risk for preterm birth or other pregnancy outcomes.  
Can be administered at birth, as routine birth-dose immunization programs already in place (e.g., BCG, hepatitis B, and polio), or just prior to the onset of the RSV season during other routine immunization visits.  
Can be administered to premature infants (at greater risk) and to infants born to unvaccinated mothers. | Administration challenges in LMIC and outside hospital settings.  
Price and potentially limited availability.  
Challenges reaching infants born in rural areas or outside of the formal healthcare system. |
Statement from the Technical Advisory Group (TAG) on COVID-19 vaccination efforts in the Americas

- Since March 2020, the Americas have reported 193 million confirmed cases of COVID-19 and 2.97 million deaths – making this the Region with the highest case fatality rate in the world.
- By May 2023, global prevalence was dominated by Omicron subvariants including XBB.1.5, XBB.1.16, and XBB.1.9. More recently, additional Omicron subvariants have emerged, such as EG.5 and BA.2.86.
- To date, the countries and territories of the Americas have administered more than 2.1 billion doses of vaccine against COVID-19. Despite this effort, only 71.3% of the population in Latin America and the Caribbean have been fully vaccinated against this disease, with differences in coverage across countries and risk groups.
- In November 2023, the number of cases is increasing again in all subregions of the Americas, except in the Caribbean, albeit at a much slower pace than at the same time in 2020 or 2021.
- After four years of pandemic, most people in the world have some immunity against the SARS-CoV-2 virus through infection, vaccination, or both. Meanwhile, significant reductions in severe disease and death related to SARS-CoV-2 have been observed across all age groups.
- At this stage of the pandemic, the benefits of a two-dose primary vaccination series have become limited.
- The TAG strongly supports the SAGE’s recommendation that countries should maintain their focus on achieving high vaccination coverage among high priority risk groups. This includes older adults, pregnant women, persons with comorbidities, immunocompromised persons, and health workers.
- Increasing the coverage rate of the primary series has a greater impact on reducing hospitalizations and deaths, compared to using the equivalent vaccine supply to increase the coverage rate of booster doses.
- Specifically:
  - Countries can reduce their morbidity and mortality rates by ensuring that all persons receive at least one dose of COVID-19 vaccine.
  - For inactivated COVID-19 vaccines (i.e., vaccines produced by Bharat, Sinovac, Sinopharm, and Valneva), two doses are required for the initial vaccine series.
  - People in the high priority groups have the highest chance of becoming seriously ill or dying. Any decrease in vaccine effectiveness, however small, increases the number of persons who experience severe illness or death. Therefore, revaccination with booster doses is recommended only for persons in the high priority groups.
  - For persons who have not yet been vaccinated against COVID-19, any of the WHO Emergency Use Listing (EUL) COVID-19 vaccines can be used for the initial dose, including monovalent XBB vaccines.
- Variant-adapted vaccines – particularly for the time being, monovalent XBB vaccines – are likely to provide some additional benefit to the index-virus only vaccines.
- Nonetheless, countries should not delay implementing vaccination while waiting for access to variant-containing vaccines. There is greater benefit in ensuring that persons at high risk
of developing severe COVID-19 receive a dose than extending this interval in anticipation of a variant-containing vaccine.
1. The countries and territories of the Americas are commended for improving their immunization coverage rates for most antigens. In 2022, the regional coverage rate for the third dose of the vaccine against diphtheria, tetanus, and pertussis (DTP3) was 83% – up from 81% in 2021 when 1.9 million children were unvaccinated. However, 1.3 million children younger than 1 year remain unvaccinated. The Region has not yet recovered its pre-pandemic coverage rates and remains far from matching its past achievements in disease control and elimination. Intense, sustained investments in the national immunization programs of the Americas remains paramount.

2. PAHO notes the recent recommendation from the WHO Strategic Advisory Group of Experts (SAGE) on Immunization for countries to consider the use of the Dengue Tetravalent Vaccine (Live, Attenuated) TAK-003 for children aged 6 to 16 years who live in settings with high dengue disease burden and high transmission intensity. In the Phase 3 vaccine trial, the vaccine efficacy (VE) of TAK-003 over 5 years was 61% (95% CI [56.0, 65.8]) against virologically confirmed dengue (VCD) and 84% (95% CI [77.8, 88.6]) against dengue-related hospitalizations. However, significant gaps regarding the safety and effectiveness of this vaccine against dengue virus type 3 and type 4 in baseline seronegative persons remain.

3. PAHO notes that the current definition of a setting “with high dengue disease burden and high transmission intensity” relies on age-specific high quality seroprevalence or incidence data for the target population, which is not readily available in countries of the Americas and would not be feasible to collect pre-vaccination.

4. Given the above considerations, PAHO does not recommend that countries implement countrywide immunization programs with the TAK-003 vaccine at this time. Also, the availability of TAK-003 vaccine doses for the Americas in 2024 and 2025 is limited.

5. PAHO urges Takeda to undertake a Phase 4 vaccine trial to address information gaps, particularly with respect to the safety and effectiveness of the TAK-003 vaccine against dengue virus type 3 and 4 in baseline seronegative persons.

6. PAHO recognizes that some countries in the Americas may wish to introduce the TAK-003 vaccine in specific subnational geographical areas where there is documented evidence of a “high dengue disease burden and high transmission intensity.” PAHO supports the SAGE’s recommendation on the introduction of the TAK-003 vaccine in these settings, provided that careful steps are taken to ensure evaluation and follow-up of the safety and effectiveness of the vaccine, and that the communities and healthcare providers involved are fully informed of the potential benefits and risks and support the use of the vaccine.
7. Hence, any introduction of the TAK-003 vaccine should be considered a pilot and be accompanied by a robust Phase 4 post-marketing study that:
   - Uses age-specific seroprevalence data or other age-specific markers of transmission intensity to identify the geographical areas with high dengue transmission intensity where the TAK-003 vaccine introduction may be considered.
   - Includes pre-vaccination serology to allow further evaluation of vaccine effectiveness and safety in baseline seronegative individuals, particularly against dengue virus type 3 and 4.

8. Before advancing with the pilot introduction and Phase 4 post-marketing study, countries should ensure that the following elements are in place and reinforced:
   - Robust dengue surveillance systems to allow the identification of suspected dengue cases and monitor disease transmission at a subnational level.
   - Robust safety surveillance systems to detect and respond to events supposedly attributable to vaccination or immunization (ESAVI).
   - Other strategies essential for the control of dengue and other mosquito-borne diseases – such as vector control, environmental care, strengthening the diagnostic capacity of laboratories, improving surveillance, and training health personnel in dengue care.
   - A clear and effective communication campaign that describes the risks and benefits of this vaccine, the importance of maintaining other public health measures to curb transmission and provides realistic expectations of the impact of TAK-003.

9. Member States considering the pilot introduction of the TAK-003 vaccine in children and adolescents should weigh the resources and opportunity costs given the need to ensure catch-up of unvaccinated children, as well as the need to recover and sustain high coverage of all current vaccines.

10. Countries that do not have a vaccination platform for adolescents (created for the administration of the vaccine against HPV, pertussis, or meningococcus) should not consider the introduction of the TAK-003 vaccine at this time. The lack of data on coadministration of these vaccines with TAK-003 constitutes a barrier to its administration in adolescents. The introduction of the vaccine in other age groups must be based on robust epidemiological data about the burden of disease, strength of infection, hospitalization, and other indicators that demonstrate that they are high-risk populations. In these cases, it should be considered that immunogenicity data (immunobridging studies) and safety – but not efficacy – data exist for persons from 17 to 60 years of age. These knowledge gaps represent another reason why it would be essential to develop Phase 4 studies.

11. PAHO welcomes the approval of Pfizer’s (Abrysvo®) Bivalent Prefusion F (RSVpreF) vaccine in pregnant women to prevent RSV disease in infants by the U.S. Food and Drug
Administration (FDA) and the European Medicines Agency (EMA), since it addresses the considerable burden of disease in infants across the Americas and specifically targets pregnant women, who are often excluded from vaccine clinical trials and therefore are delayed in reaping their benefits.

12. PAHO is encouraged by the results of the Phase 3 Maternal Immunization Study for Safety and Efficacy (MATISSE) study, which suggest high vaccine efficacy against severe RSV-associated disease in infants from birth through 6 months. In the trial, over 7000 pregnant women from 18 countries were included in the study. However, data were collected only from upper-middle-income countries (UMIC) and high-income countries (HIC). The impact study recommended by the SAGE in its October 2022 meeting in lower-middle-income countries is urgently needed to confirm the findings on vaccine safety and efficacy the MATISSE study outside of UMIC and HIC settings.

13. PAHO notes the high cost of the RSVpreF vaccine in the United States and urges the PAHO Procurement and Supply Management Department and the PAHO Revolving Fund to negotiate a lower price for countries in the Americas to avoid inequitable implementation of this vaccine into the national immunization programs of the Region.

14. The PAHO assesses that maternal RSVpreF vaccine is best given in pregnant women at 32–36 weeks of gestation to prevent RSV disease in infants while minimizing the risk of preterm birth. Any introduction of maternal RSVpreF vaccine should be accompanied by:
   • Identification of the optimal timing of vaccine administration according to country-specific RSV seasonality patterns
   • Robust vaccine effectiveness and impact studies
   • Well-designed safety, cost-effectiveness, economic burden, and affordability studies
   • Studies of behavioral and social factors to facilitate vaccine uptake
   • Integration with other prenatal immunization programs (e.g., influenza), services, and outreach operations
   • Careful balance between the resources needed for the introduction of this vaccine and the requirements and goals of existing vaccination programs (e.g., maintaining measles elimination)
   • Documentation of the programmatic challenges of new vaccine introduction, especially in the context of a recovering national immunization program and limited financial resources.

15. COVID-19 infection remains one of the leading causes of respiratory disease and death in the Americas. PAHO welcomes the updated WHO Roadmap on COVID-19 vaccination. Any of the WHO Emergency Use Listing (EUL) COVID-19 vaccines, including monovalent XBB vaccines, can be used for the initial dose and for revaccination. The priority use groups are the oldest adults, older adults with comorbidities, pregnant women, healthcare workers, and immunocompromised persons.


