Hepatitis E vaccines background paper

Strategic Advisory Group of Experts (SAGE) on Immunization meeting

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1. Background

Hepatitis E virus (HEV) is a common cause of enterically transmitted viral hepatitis. Human HEV, a member of family Hepeviridae and genus *Orthohepevirus A*, has four major genotypes that cause human disease (genotypes 1, 2, 3 and 4), which belong to one serotype. The genotypes have distinct routes of transmission and geographical distributions. HEV genotypes 1 and 2 primarily infect humans, whereas genotypes 3 and 4 mainly infect non-human mammals and cause occasional zoonotic disease in humans. Genotype 1 and 2 is mainly faecal-orally transmitted, in particular faecal contamination of drinking water. The transmission of genotypes 3 and 4 is mainly zoonotic, through consumption of uncooked or undercooked meat, with the environment also a likely source of infection. The infection can occur as outbreaks or as sporadic cases. Genotypes 1 and 2 are the most prevalent HEV genotype in Africa and parts of Asia and may lead to large-scale outbreaks, often in settings with underlying endemic viral circulation. These outbreaks particularly occur in overcrowded, low-income settings with inadequate access to clean water and disposal of human feces. Those living in fragile, conflict-affected settings and vulnerable populations, especially refugees or internally displaced persons (IDP) are disproportionally affected. Environmental conditions such as flooding and heavy rainfalls, linked to poor sanitary conditions, often facilitate the spread of the virus *(1-3)*. While sporadic cases and travel-related infections occur, HEV remains a disease of poverty.

In 2005, Rein et al. *(4)* estimated a total of 20.1 (95% credible interval (Cr.I.).: 2.8-37.0) million incident HEV infections in pre-defined regions for which genotype 1 (and to a lesser extent genotype 2) HEV was dominant: Asia Central, Asia East, Asia South, Asia Southeast, North Africa and the Middle East, Sub-Saharan Africa Central, Sub-Saharan Africa East, Sub-Saharan Africa Southern, and Sub-Saharan Africa West. These nine regions contained approximately 4.7 billion people or 72.8% of the global population in 2005. The 20.1 million infections resulted in 3.4 (95% Cr.I.: 0.5-6.5) million (17.0%) cases of symptomatic illness and 70,000 (95% Cr.I.: 12,400-132,732) deaths.

Based on 2019 Institute for Health Metrics and Evaluation (IHME) Global Burden of Disease data, acute hepatitis E resulted in 131 000 global disability-adjusted life years (DALYs) (95% uncertainty interval (UI): 84 600–191 000) in 2019 and was responsible for 3% (95% UI 2.1–4) of acute hepatitis DALYs. Incidence was estimated to be 19.5 million (95% CI: 16-23) and 1930 deaths in 2019 according to the global burden of disease study *(5)*.

In 2023, a systematic review of global hepatitis E outbreaks to inform response and coordination initiatives *(6)* was conducted. The number of confirmed cases per outbreak ranged from 5 to 4,085 (not including pregnant women) and confirmed cases among pregnant women ranged from 3 (out of 278 suspected cases) to 211 (out of 576 suspected cases). The duration of the outbreaks varied from 4 weeks to 3 years. Approximately 50% of the outbreaks occurred in camp settings (e.g., refugee camps or internally displaced person camps). The authors noted considerable under-reporting and several significant data gaps.

Clinical presentation of disease may include asymptomatic infection, nonspecific viral syndrome, anicteric and icteric hepatitis, and fulminant, at times fatal, acute liver failure (ALF). In particular, pregnant women have a high risk of severe disease, and the case fatality rate in this population has been reported to be up to 25% *(7, 8).* Further risk factors for HEV infection include environmental factors such as exposure to contaminated water, unsanitary/ lack of toilets and exposure to sewage. Animal contact

(occupational exposure) and consumption of certain foods (mainly insufficiently cooked pork or pig liver product) is also associated with an increased risk of HEV infection *(9)*. Last, immunosuppression, blood transfusion, dialysis or hemodialysis and solid organ transplantation are correlated with the development of HEV infection *(9, 10)*. In individuals with chronic hepatitis B, HEV infection may result in an acute exacerbation of their liver disease *(11)*.

There is no causal treatment against the disease, only symptomatic. Beyond Water, Sanitation and Hygiene (WASH), vaccination serves as preventive measure. There is currently one vaccine available. HEV 239 (Hecolin®) has been licensed for use in healthy adults aged ≥16 years in China since 2011 via intramuscular injection using a 3-dose schedule (0, 1 and 6 months). HEV 239 is a subunit vaccine, containing a recombinant protein corresponding to viral capsid protein from HEV genotype 1, with alum as an adjuvant. The product is supplied in a pre-filled syringe with an approved shelf life of at least 36 months (and up to 45 months under appropriate storage conditions).

To date, beyond China, the vaccine has been licensed in Pakistan in 2020, and registration processes are ongoing in other countries (India, Nepal and Indonesia). Hecolin® has not yet been submitted for WHO Prequalification (PQ). Xiamen Innovax Biotech (Wantai BioPharm), which received PQ for their bivalent HPV vaccine in 2021, indicated the company's intent to submit a new formulation of the product (removal of thiomersal) and a new presentation (1-dose vial) for consideration by WHO PQ after the startup of new manufacturing facilities and approval by the national regulatory authority (National Medical Products Administration (NMPA), China) in 2026-2027. A second recombinant Hepatitis E vaccines developed by Zydus Lifesciences Ltd. is currently in clinical study phase.

HEV 239 has proven to be safe, immunogenic and highly efficacious among healthy adults aged 16-65 years old. In a large Phase III randomized trial with more than 100 000 participants, the primary (per protocol) analysis revealed 100% vaccine efficacy (95% CI: 72.1–100%; p<0.0001) during the 12 months after the third dose *(12, 13).* The Phase III trial was extended to assess the long-term efficacy of the vaccine. After 4.5 years, efficacy did not significantly decrease during the extended follow-up period and was determined to be 93% (95% CI: 78.6-97.9%) among participants having received all three doses, and 85% (95% CI: 67.1-93.3%) among those with at least one dose *(14)*. After 10 years follow-up, vaccine efficacy remained at 83.1% (95% CI 69.4–91.4%) *(15)*.

In 2014, the Global Advisory Committee on Vaccine Safety (GACVS) assessed HEV 239 vaccine safety derived from the clinical trial data *(16)*. These data suggest that the vaccine is well tolerated. Short-term local and systemic solicited adverse event data showed more frequent local adverse events in the HEV 239 group compared to the control group. The solicited systemic adverse events and unsolicited adverse events occurred at similar rates between study groups. There appeared to be no difference in serious adverse events or deaths identified in the HEV 239 group compared to the control group.

Recent data show that 96.7% of vaccinated elderly aged >65 years seroconverted at one month after the final dose *(17)*. Vaccine safety and immunogenicity of Hecolin® in hepatitis B surface antigen (HBsAg) positive adults, who have a higher risk of poor prognosis after super-infection with HEV, is very similar to that of HBsAg negative adults *(18)*.

HEV strains that infect humans belong to one currently identifiable serotype, with marked serological cross-reactivity as well as evidence for cross-protection in non-human primates and in humans *(19-21)*. Therefore, HEV vaccine with recombinant pORF2s, such as HEV 239, derived from a given genotype is expected to provide cross-genotype protection against all four genotypes *(22)*. In the Phase III trial, of 23 persons who developed HEV infection (22 in the placebo group and 1 in the vaccine group), viral genotype could be studied in 13 patients. Of these 13 isolates (all in the placebo group), 12 were genotype 4 and one was genotype 1 *(12)*. Within this trial, HEV 239 induced protection can be assumed mainly against infection with HEV genotype 4.

In 2015, WHO recommended using the vaccine in special situations such as outbreaks where the risk of hepatitis E or of its complications or mortality is particularly high *(23)*. In particular, the use of the vaccine to mitigate or prevent outbreaks of hepatitis E should be considered as well as the use of the vaccine to mitigate consequences in high risk groups such as pregnant women.

To date, WHO does not make a recommendation on the introduction of the vaccine for routine use in national programmes due to absence of sufficient information, in particular on vaccination of recipients <16 years of age, immunosuppressed patients, and on the degree of cross-protection the vaccine may confer. However, national authorities may decide to use the vaccine based on the local epidemiology *(23)*.

SAGE was last informed on Hepatitis E vaccine during a session in October 2021 *(24)* with a focus on new data and recent developments that have emerged since the issuance of the 2015 WHO vaccine position paper. SAGE highlighted that the importance of the vaccine to mitigate the impact of hepatitis E outbreaks and underlined its contributions to increase equity as those affected by hepatitis E are often underprivileged populations in low-resource settings. In order to ensure that timely availability of the hepatitis E vaccine, SAGE recommended the support and establishment of a vaccine stockpile.

In March 2022, a significant milestone in the field of Hepatitis E vaccination was achieved on the African continent. In response to a hepatitis E outbreak in Bentiu, South Sudan, Médecins Sans Frontières supported the South Sudan Ministry of Health to implement a Hepatitis E vaccination campaign. Three vaccination rounds were conducted, immunizing more than 24,000 people per round, including pregnant women *(25)*. This was the first ever use of the vaccine to mitigate the consequences of an outbreak, as recommended by WHO in the 2015 Hepatitis E vaccine position paper *(23)*.

In October 2023, the Governance Oversight Committee of the International Coordinating Group (ICG) approved an initial “proof-of-concept” (PoC) global Hepatitis E vaccine stockpile under the ICG mechanism. The PoC stockpile will be established in 2024 for a 3-year period (2024-2026).

In March 2024, SAGE will be asked to advise on the risk-benefit of vaccination of pregnant women in the contexts of outbreaks occurring in fragile and conflict-affected settings. Further, SAGE will be asked to recommend on whether less than the manufacturer-stipulated 3 doses schedule could be considered in special situations, such as outbreak and fragile and conflict affected settings, where providing a full schedule has proven to be difficult for a number of reasons including population movement.

2. Vaccination with less than a full dosing schedule

2.1. Ask to SAGE

SAGE is asked to reflect on the totality of data on alternative schedules and to recommend on their impact to mitigate the consequences of outbreaks in fragile and conflict-affected settings.

2.2. Review of Immunogenicity, Efficacy and Effectiveness of Shorter Schedules of Hepatitis E Vaccine

1. Introduction

HEV 239 (Hecolin®; Xiamen Innovax Biotech Co., Ltd., China) is the only licensed vaccine against hepatitis E available worldwide. It contains a recombinant 239-aminoacid protein corresponding to amino acids 368-606 of the capsid protein of hepatitis E virus (HEV), expressed in *Escherichia coli,* as virus-like particles. This vaccine received approval from the China Food and Drug Administration in December 2011, and was also approved in Pakistan in 2021. It is recommended for use as three intramuscular doses of 0.5 ml (containing 30 µg of purified recombinant HEV antigen, sodium chloride, disodium hydrogen phosphate, potassium dihydrogen phosphate, 0.8 mg aluminium hydroxide, 25 µg thiomersal, and water for injection) each at 0, 1 and 6 months among persons aged 16 years or above and at a high risk of contracting HEV infection, such as those working with animals, food handlers, students, members of the armed forces, pregnant women, and visitors to endemic areas.

The three-dose regimen of HEV 239 vaccine is known to induce a strong antibody response, which has been shown to be protective for 10 years (Huang *et al,* 2024). However, the schedule of administration is quite prolonged, making its implementation less feasible and challenging in situations such as during hepatitis E outbreaks due to population movement, and in emergency responders and humanitarian workers where a quick protection is desired.

In 2022, the Ministry of Health (MoH) in South Sudan and Médecins Sans Frontières (MSF) implemented the first mass reactive vaccination campaign against hepatitis E in Bentiu IDP camp, South Sudan. A vaccination campaign was conducted in three rounds in March, April and October 2022 targeting 26,848 residents of Bentiu IDP camp aged 16–40 years old, including pregnant women *(26)*.

In terms of coverage, 86% (95% CI 84–88%) of the vaccine-eligible population received at least one dose, 73% (95% CI 70–75%) at least two doses and 58% (55-61%) three doses. Nesbitt and al. *(26)* concluded that with limited employment opportunities and food availability in Bentiu IDP camp, residents frequently seek opportunities outside the camp, and many individuals maintain a second residence in their county of origin. Temporary absence was common accounting for over 50% of non-vaccination among individuals vaccinated at least once, and 55% among those with two doses. Most reasons for non-vaccination were related to absence rather than fear of needles or side effects reflecting a general positive attitude towards vaccination in the community. Population mobility was considered a challenge

for accurately estimating population size and providing a multi-dose vaccination schedule over a six-month period.

Hence, there is a need for shorter regimens; these will not only be more practical but also more cost-effective.

This review collates the available data on immunogenicity, efficacy/effectiveness, and the duration of protection following HEV 239 vaccine when administered in a schedule with fewer than three doses or one with shorter time interval between doses.

2. Methodology

Relevant articles were identified by searching several databases [Medline OvidSP (1946-present), EMBASE, Cochrane CENTRAL, PubMed (1946-present) and International Clinical Trials Registry Platform-ICTRP], using the following search terms: 'Hepatitis E vaccin*', 'HEV 239', 'Hecolin', 'Hepatitis E/immunology', 'Hepatitis E/prevention and control' and 'Hepatitis E virus/immunolog*' on February 22, 2024. Titles and abstracts of the articles so identified were screened using the inclusion and exclusion criteria in Box 1.

In addition, the vaccine manufacturer, and other partners were contacted to obtain additional published and unpublished information.

Box 1: Inclusion and exclusion criteria applied to the results of literature search

Inclusion criteria

- Articles that include data on immunogenicity, efficacy or effectiveness of *Escherichia coli* expressed HEV 239 virus-like particle (VLP) recombinant protein vaccine (Hecolin®), stratified by type of shortened schedule received (number of doses, time periods)
- Clinical trials and post-licensure observational studies
- Populations: All
- Languages: No language restriction

Exclusion criteria

- Not hepatitis E vaccine or Hecolin® vaccine
- Non-human studies
- Pre-clinical studies, systematic reviews, and grey literature

The initial search identified a total of 47 records. After screening their titles and abstracts, 14 sources were identified for full-text assessment. Of these, seven data sources [six papers and one unpublished dataset (from clinicaltrials.gov) met the inclusion criteria and these data were further analyzed. **Table 1** contains a summary of those data sources that were further analyzed. A list of studies that were excluded are shown in **Annex 1**. The GRADE and Evidence to Decision (E2D) assessments are shown in **Annex 2**.

Table 1: List of studies identified for inclusion in this review

Author, year; location	Brief description	Type of data included	Number of planned doses/schedules	Subjects	Number of subjects
During initial vaccine development					
Zhang *et al*, 2009; China *(13)*	Phase II study	Immunogenicity, efficacy	2 doses (0, 6 mo) vs 3 doses (0, 1 and 6 mo)	Seronegative	457
Zhu *et al*, 2010; China *(12)* Zhang *et al*, 2015; China *(14)* Huang *et al,* 2024; China *(15)*	Phase III study Longer term follow-up (4.5 years) of phase III study Longer term follow-up (10 years) of phase III study	Immunogenicity, efficacy	3 doses (0, 1 and 6 mo)	Irrespective of serostatus (47% seropositive)	112,604
Post-licensure studies					
Unpublished: Clinicaltrials.gov ID NCT03827395; USA *(27)*	Phase I study for the United States population	Immunogenicity	3 doses (0, 1 and 6 mo)	Seronegative	25
Chen *et al*, 2019; China *(28)*	Clinical trial of a 3-dose accelerated schedule (0,7 and 21 days)	Immunogenicity	3 doses in an accelerated (0, 7 and 21 days) vs usual (0, 1 and 6 mo) schedule	Seronegative	126
Øverbø *et al*, 2023; Bangladesh *(29)*	Clinical trial of a 2-dose schedule, versus a 3-dose schedule of hepatitis B vaccine	Immunogenicity, efficacy	2 doses (0 and 1 month)	Irrespective of serostatus (33% seropositive)	100

3. Immunogenicity

The data on immunogenicity of fewer than three doses or shorter regimens of HEV 239 vaccine in humans are available from the phase II *(13)* and phase III *(12, 14, 15)* trials during the initial vaccine development, and from three other studies *(27-29)*.

Though anti-HEV antibodies are believed to be protective against HEV infection, the antibody titer defining the protection threshold remains unknown. Retrospective analysis of data from the large phase 3 randomized placebo-controlled trial of HEV 239 vaccine, suggested that anti-HEV levels exceeding 1.0 WHO Units [WU]/mL, as measured by an enzyme-immunoassay (Wantai, Beijing, China; seropositivity threshold = 0.154 WU/mL; based on a dimeric E2 antigen which resembles the protein contained in the HEV 239 vaccine) at month 7 (i.e. one month after the third dose) conferred better protection that those below this cut-off *(30)*. However, the dose–effect relationship was not perfect.

3.1 *Initial Phase II study*

This study included healthy persons aged 16-65 years (33% women) who tested negative for anti-HEV antibodies *(13)*. It had two components: a dose-scheduling study to determine the optimum number of vaccine doses and a dose-escalation study to determine the optimum amount for each. In the dose-escalation study, larger doses (20, 30 and 40-μg each) had significantly better immunogenicity than the 10-μg dose when administered in a 3-dose (0, 1 and 6 mo) schedule. The geometric mean titer of anti-HEV antibody following the 30-μg dose schedule (n=41) was somewhat higher than that with the 20-μg dose schedule (n=49) (18.4 vs 15.9 WU/ml), though the difference was not statistically significant.

In the dose-scheduling study, 457 subjects (mean age: 32.8±12.5 years) were randomly assigned to receive two doses (20-μg each, at 0 and 6 months) of HEV 239, three doses (20-μg each, at 0, 1 and 6 months) of HEV 239, or three doses of hepatitis B vaccine (5-μg each, at 0, 1 and 6 months; control group) by intramuscular injections. Immunogenicity was assessed using seroconversion rates and geometric mean concentrations (GMC) of anti-HEV antibody, using the Wantai anti-HEV assay at months 0 (baseline), 2 (one month after the second dose in the 3-dose group), 6 (before the final dose), 7 (one month after the final dose) and 13 (7 months after the final dose).

The two-dose schedule of HEV 239 was found to have a seroconversion rate at 7 months similar to that with the three-dose schedule (98% vs 100%) (**Table 2**). However, it was associated with significantly lower anti-HEV antibody titers [GMC (95% CI) = 8.6 (6.5-11.3) WU/ml], than the three-dose schedule [15.9 (13.8-18.2); $p<0.05$) (**Figure 1**). In individuals who received three doses of HEV 239, GMC at month 2, i.e. one month after the second dose, was 1.8 (1.6-1.9) WU/ml; individuals receiving two-dose schedule were not tested at this time-point. It is noteworthy that each dose in both the groups was 20 μg and not the currently recommended 30 μg dose.

Table 2: Results of seroconversion and antibody titers at 7 months after starting vaccination in the phase II trial of HEV 239 vaccine (from Zhang et al, 2009 *(13)*)

Vaccine administered and the dose schedule	n	Seropositivity (%)	IgG anti-HEV, WU/ml; Geometric mean concentration (95% CI)
HEV 239; 20 μg X 3 doses (0, 1 and 6 months)	128	100	15.9 (13.8-18.2)
HEV 239; 20 μg X 2 doses (0 and 6 month)	109	98	8.6 (6.5-11.3)
HBV vaccine; 5 μg X 3 doses (0, 1 and 6 months)	131	8	-

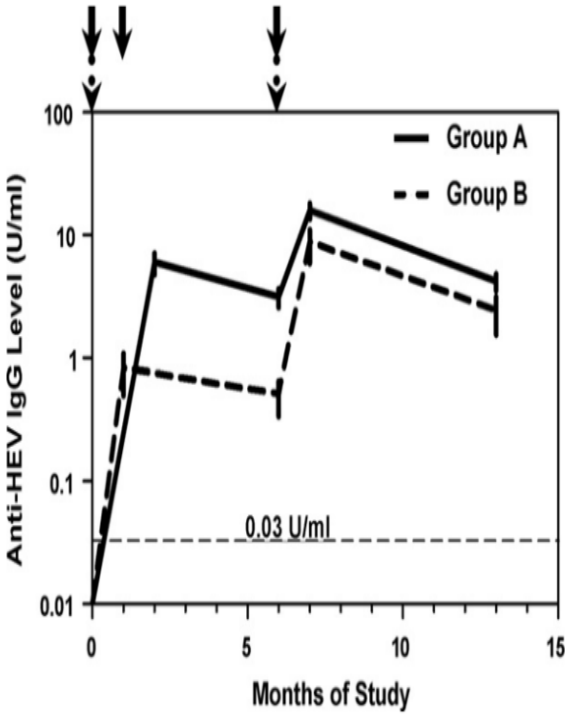


Figure 1: Antibody response after HEV 239 vaccination during 13 months of follow-up: Group A: three-dose schedule (0, 1 and 6 mo); Group B: two-dose schedule (0 and 6 mo). Mean IgG anti-HEV levels and 95% CI are depicted.

3.2 *Phase III study (the licensure trial)*

In this large clinical trial in a field setting in China *(12, 14, 15)*, 112,604 healthy adults of either sex aged 33-56 years (mean±SD age = 44.7 ±11.1 years; 56.5% female), irrespective of their HEV serostatus (47% seropositive at baseline) were randomized to receive three intramuscular doses (at 0, 1 and 6 months) of either HEV239 (30-μg each) or a hepatitis B vaccine (5-μg each), and were followed up for safety and efficacy (occurrence of clinical hepatitis E) for 48 months beginning one month after the administration of the third dose. In addition, in a subset of 11,165 subjects ('the immunogenicity subset'; including n=5567 in the HEV 239 arm and n=5,598 in the comparator HBV vaccine arm), blood specimens were collected at various time points up to 55 months after the first dose and tested for anti-HEV antibody titers using Wantai quantitative assay.

Of the 5567 persons in the HEV 239 arm in the immunogenicity subset, some failed to complete the intended 3-dose schedule. Thus, 184 (3.3%) subjects missed the third dose (receiving two doses at 0 and 1 months) and 189 (3.4%) missed the second dose (receiving the first and the third dose at 0 and 6 months). For these participants, data at the 43-month follow-up were available for 117 and 125 participants, respectively (there were too few subjects available at 55 months); results of seropositivity for anti-HEV at this time point and GMC at various time points of subjects who had received two or three doses are shown in **Figure 2** and **Table 3**.

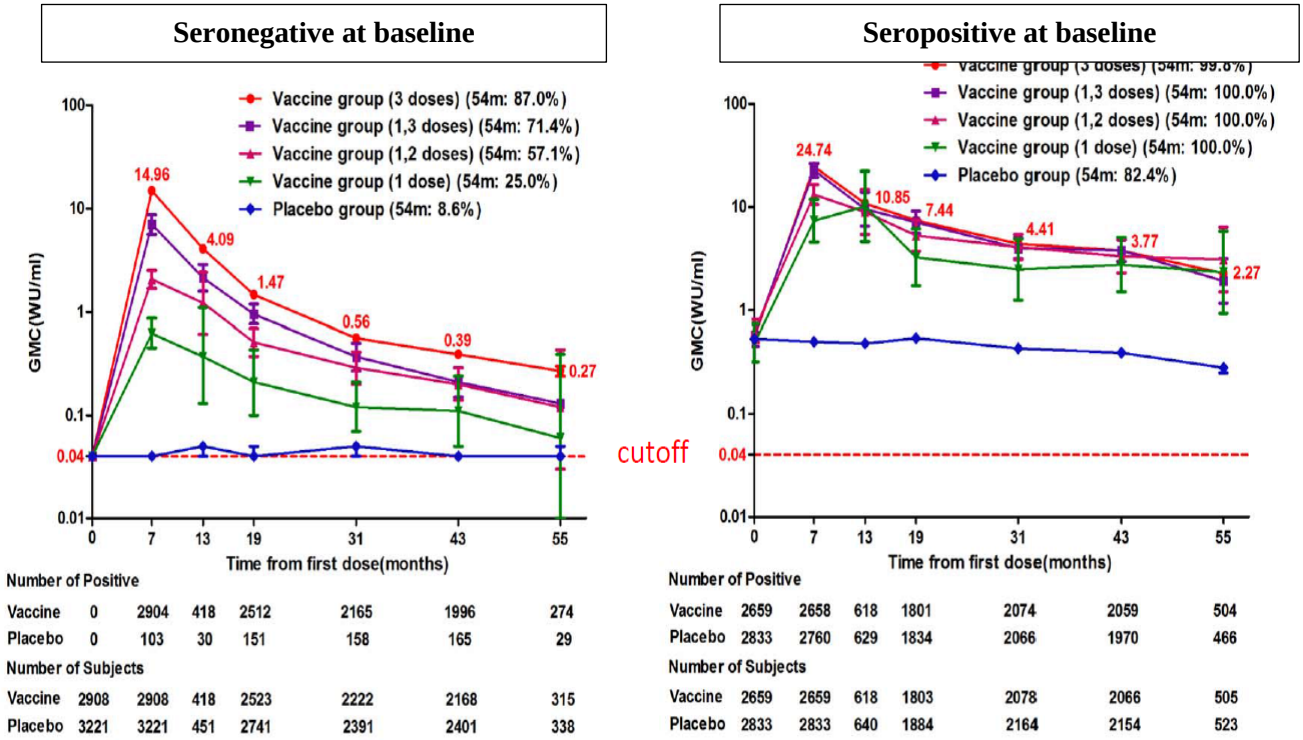


Figure 2: Geometric mean concentration of IgG anti-HEV and seropositivity rates among participants in immunogenicity sub-group

Table 3: Results of seroconversion and antibody titers at 7 and 44 months after starting vaccination in the phase III trial of HEV 239 vaccine (from Zhu et al., 2010, Zhang et al., 2015 *(12, 14)*)

Number of doses received and time since the first dose	Three doses (0, 1, 6 mo)	Two doses (0, 1 mo)	Two doses (0, 6 mo)	One dose (0 mo)
Seronegative at baseline				
Seropositivity rate				
7 mo	99.9%	98%	100%	98%
13 mo	100%	100%	100%	100%
43 mo	92%	82%	80%	39%
Antibody titer (WU/ml), GMC (95% CI)				
7 mo	14.96 (14.48-15.45)	2.06 (1.68-2.51)	7.03 (5.67-8.72)	0.62 (0.45-0.87)
13 mo	4.09 (3.81-4.39)	1.22 (0.61-2.43)	2.13 (1.58-2.87)	0.37 (0.13-1.11)
43 mo	0.39 (0.37-0.41)	0.20 (0.14-0.29)	0.21 (0.15-0.29)	0.11 (0.05-0.24)
Seropositive at baseline				
Seropositivity rate				
7 mo	-	-		-
43 mo	99.8%	100%	100%	100%
Antibody titer (WU/ml), GMC (95% CI)				
7 mo	24.74 (14.74-34.74)	15.01 (12.01-17.01)	24.54 (14.54-34.54)	9.01 (7.01-10.01)
43 mo	3.77 (2.77-4.77)	2.77 (1.77-3.77)	3.57 (2.57-4.57)	2.00 (1.34-2.77)

Though this comparison was not a randomized one, these data provide useful information about the expected response to two doses. It may be pertinent to note that data for the former two-dose subset (0, 1 month) is of greater relevance in relation to a shorter-duration schedule than that of the latter two-dose subset (0, 6 month). Further, the results were dissimilar among persons who were seropositive for anti-HEV and those who were seronegative at baseline, and hence have been presented separately.

In individuals with baseline anti-HEV seropositivity, GMC levels remained high even at 43 months of follow-up irrespective of the number of doses received. These data would probably indicate that even two doses of HEV 239 vaccine, could provide durable protective antibody levels in HEV endemic regions.

By contrast, in individuals who were seronegative for anti-HEV at baseline, the peak anti-HEV levels were lower with each dose schedule, and these declined over time with the levels at 43 months being lower in those receiving two doses as compared to those receiving three doses. However, even in those receiving two doses, the antibody levels were quite high till 13 months of follow-up.

3.3 *Phase I study in the United States*

In a phase I study done in healthy volunteers in the US *(27)*, done in 2019, 25 individuals (age: 18-45 years, 19 [76%] women, all seronegative for anti-HEV antibody at baseline) were randomized into 2 groups: HEV 239 vaccine (n=20) and placebo (n=5) given intramuscularly at 0, 1 and 6 months. They were followed up to 6 months after the 3rd dose. The seropositivity at 1 month after the second dose was 100% and GMC was 6.16 (1.68-18.77) WU/ml. These anti-HEV levels were only slightly lower [11.5 (2.72-33.02)] WU/ml than those achieved 1 month after the third dose.

3.4 *Two-dose schedule study*

In a randomized, controlled trial in Bangladesh, designed to study two-dose HEV 239 schedule (Øverbø *et al*, Vaccine 2023), 100 individuals (mean age = 26.1±9.6 years; 52% males; 33% seropositive for hepatitis E antibody at baseline) were randomised 1:1 to receive two doses (at 0 and 1 month) either of HEV 239 or of hepatitis B vaccine intramuscularly and followed up to 23 months after the last dose. The seropositivity rates in the HEV 239 group at 2 months and 24 months from the administration of first dose were 100% and 98%, respectively. The GMC at 2 and 24 months were 49.5 (31.5-77.7) WU/ml and 6.4 (3.6-11.3) WU/ml, respectively (***Table 4***).

Table 4: Results of seroconversion and antibody titers at 2 and 24 months after starting vaccination in the Bangladesh trial of HEV 239 vaccine (from Øverbø et al, 2023 *(29)*)

Time since the first dose	Seropositivity rate	Antibody titer (WU/ml), GMC (95% CI)
Overall (n=50)		
2 months	100%	49.5 (31.5-77.7)
24 months	98%	6.4 (3.6-11.3)
Seropositive at baseline (n=20)		
2 months	100%	189.3 (122.3-293.1)
24 months	100%	36.1 (23.2-56.4)
Seronegative at baseline (n=30)		
2 months	100%	20.2 (12.6-32.5)
24 months	95%	1.6 (1.0-2.5)

Unfortunately, this study did not have a group with the three-dose schedule, and hence no data for head-to-head comparison of 2-dose schedule vs 3-dose schedule of HEV 239 were available.

3.5 *Three-dose accelerated schedule*

A randomized trial in China *(28)* has assessed the immunogenicity of an acceralated HEV 239 schedule administered over three weeks. In this trial, 126 health individuals (age: mean ± SD = 49.83±10.67 years; 48% male), seronegative for anti HEV, were randomized in 1:1 ratio to receive three doses of HEV 239, either in an accelerated schedule (0, 7 and 21 days; n=63) or the routine schedule (0, 1 and 6 months; n=63), and were followed up for seven months from the first dose. At seven months from the first dose, seropositivity was 100% in both the groups, whereas GMC was somewhat lower with the accelerated schedule [5.0 (4.5-6.5) WU/ml] than the routine schedule [9.5 (8.0-10.1) WU/ml]. The GMC antibody titer after the second dose of the routine schedule was 5.0 (4.0-6.0) WU/ml; data after the second dose of the accelerated schedule were not provided.

4. Vaccine efficacy

4.1 *Initial Phase II study*

Though this study was not meant to primarily assess vaccine efficacy, the investigators did assess the occurrence of new HEV infections *(13)*. For this, the study participants who had received three-dose schedule of HEV 239 vaccine (20-µg each at 0, 1, and 6 months; n = 155), two-dose schedule of HEV 239 (20-µg each at 0 and 6 months; n = 151), or three-dose schedule of a control vaccine (hepatitis B vaccine; 0, 1 and 6 months; n = 151) were followed up for serological evidence of HEV infection during 7 to 13 months after the last dose. HEV infection was defined as the occurrence of a greater than three-fold rise in the levels of IgG anti-HEV antibody in paired sera, while ignoring any rise that occurred during the first seven months from the first dose in those receiving HEV 239 vaccine (irrespective of the number of doses) since these could be attributed to the effect of the vaccine itself.

In all, nine episodes of HEV infection were recorded in the control group and one each in the two-dose and the three-dose HEV vaccine groups. All these episodes were sub-clinical, with none of the subjects reporting symptoms suggestive of hepatitis. Thus, the efficacy following the two-dose schedule was 85 % (95% CI = 10% to 99%), being comparable to the 89% (31% to 100%) efficacy of the three-dose schedule.

4.2 *Phase III study (the licensure trial)*

This is the only study that has primarily assessed the efficacy of the HEV 239 vaccine. In this study, 112,604 healthy persons in China between the ages of 16 and 65 years were randomly assigned to receive three 30-µg doses of the HEV 239 vaccine at 0, 1, and 6 months, or a placebo (hepatitis B vaccine) *(12)*. An active hepatitis monitoring system was used to monitor the study participants.

The primary efficacy analysis (per protocol) compared the rate of hepatitis E illness among participants who had received three doses of vaccine or placebo, during the period from one month after the third dose till the end of follow-up. Hepatitis E illness was defined by: (i) occurrence of constitutional symptoms (fatigue, appetite loss or both) lasting at least three days; (ii) serum ALT elevation (at least

2.5-fold the upper limit of normal range) and (iii) evidence of recent HEV infection (at least two of the following markers: positive anti-HEV IgM or HEV RNA; and a ≥4-times increase in anti-HEV IgG concentration).

In an extension of the original study, the subjects in this trial were followed up for 120 months (that is 113 months beginning one month after the last dose at 6 months) in the per-protocol subset to obtain data on long-term efficacy *(15)*. In this extension component, in addition to the study participants, residents in the 11 townships covered by the surveillance system who were not enrolled in the trial and had been born between 1941-1991 (in keeping with the participant group) were also included as an external control cohort (n=178,236) to further evaluate vaccine efficacy (Huang *et al*., 2024).

In the per protocol analysis (which included only those participants who received three doses of HEV 239), efficacy of HEV 239 was 89% (76% to 96%) at 102 months and 87% (73% to 94%) at 120 months of follow-up. In a modified intention-to-treat analysis (which included those participants who had received any dose of HEV 239 vaccine and followed up for efficacy up to 120 months from the beginning of vaccination), efficacy remained above 82% in the prolonged follow-up (102 months: 85% (72% to 93%) and 120 months: 83% (69% to 91%).

An additional analysis evaluated vaccine efficacy after two doses (at 0 and 1 months) of the vaccine, by including data (a) for those participants (n=3542) who received only two doses (followed-up from 15 days after the second dose up to 120 months) for the entire follow-up period, and (b) for the participants (n=48,693) who received three doses during the follow-up period beginning 15 days after the second dose till 6 months after the first dose (i.e. when they received the third dose). The participants (n=250) who had received only the first and the third doses (i.e. two doses at 0 and 6 mo) were excluded from analysis. During the time period between 1.5 months to 30 months (beginning 15 days after the second dose), six cases of acute hepatitis E were recorded among placebo recipients (n=3765 between 6 months to 30 months, and n=52,428 till administration of the third dose) and none among the HEV 239 vaccine recipients (n=3542 between 6 months to 30 months, and n=52,235 till administration of third dose), indicating an efficacy of 100.0%, albeit with broad 95% confidence intervals (15.4% to 100.0%) *(15)*.

During the follow-up from 30 months to 120 months after the start of vaccination, the number of new hepatitis E cases in the placebo group was too few, leading to inadequate statistical power for estimation of long-term efficacy of the two-dose regimen. However, a comparison of the number of cases among HEV vaccine recipients with that in the external control cohort showed a high efficacy (standardized for age and sex) rate (Table 5); however, this comparison represents post-hoc observational data, which may be subject to various forms of confounding and bias.

Table 5 :Long-term vaccine efficacy in participants administered with two doses (first and second dose) (from Huang et al., 2024 *(15)*)

Time since the second dose (months)	Disease incidence (per 100,000 person years)			Vaccine efficacy, % (95%CI)			
	HEV 239 vaccine group (n=3,542)	Placebo group (n= 3,765)	External control group (n=178,236)	Vaccine vs placebo		Vaccine vs external control cohort*	
1.5-30	0.0	2.3	2.0	100	(+15.4 to 100.0)	100	(31.1 to 100.0)
1.5-54	0.3	1.8	2.1	83.4	(–36.7 to 99.6)	85.7	(19.1 to 99.6)
1.5-78	0.2	1.5	2.0	83.4	(–36.5 to 99.6)	88.1	(32.8 to 99.7)
1.5-102	0.2	1.5	1.9	85.8	(–10.4 to 99.7)	89.1	(39.0 to 99.7)
1.5-120	0.2	1.3	1.8	85.8	(–10.4 to 99.7)	89.9	(43.4 to 99.7)

*Post-hoc analysis; standardized for age and sex

4.3 *Two-dose schedule study*

In the Bangladesh trial to assess the two-dose schedule of HEV 239 versus two doses of HBV vaccine *(29)*, 100 individuals were randomised into two groups (n=50 each). They were followed up to 23 months after the last dose for episodes of HEV infection. A greater than three-fold increase in the level of IgG anti-HEV antibody in paired sera was taken as evidence for HEV infection. Five cases of HEV infection were noted in the control group (n=45) and none in the HEV 239 vaccine group (n =43) [efficacy-100% (82-100%) to prevent subclinical hepatitis E infection].

5. Conclusions on the use of shorter schedules

- Data on immunogenicity, efficacy and effectiveness of shorter schedules of HEV 239 vaccine are limited.
- The two-dose (0 and 1 month) and the accelerated (0,7 and 21 days) schedules showed rapid and strong anti-HEV antibody response that remained detectable for at least two years.
- In individuals who are seropositive for anti-HEV antibodies at baseline show a durable antibody response irrespective of the number of HEV 239 vaccine doses, which appears to last for beyond 8.5 years.
- In individuals who are seronegative for anti-HEV antibodies at baseline, administration of two doses of HEV 239 leads to an antibody response which is somewhat lower than that observed in seropositive individuals and declines over time. However, even in these individuals, the antibody levels appear to remain substantially high till at least 13 months of follow-up, which could be useful in outbreak control situations or other situations where a shorter vaccine schedule is desirable.
- The available data indicate that two doses of HEV 239 administered one month apart confer good protection against hepatitis E at least in the short term.

3. Risk-benefit of vaccination during pregnancy

3.1. Ask to SAGE

SAGE is asked to advise on the public health value of HEV vaccination and to recommend on the risk-benefit of vaccinating pregnant women in the context of outbreaks and fragile and conflict affected settings.

3.2. Evidence

3.2.1. Disease severity of HEV during pregnancy

Pregnant women, in particular in the second or third trimester of gestation, are at a greater risk for development of symptomatic disease than are nonpregnant women and men and carry a greater risk for progression to ALF, as compared with nonpregnant persons with hepatitis E *(31)*. HEV infection in pregnancy is also associated with an increased risk for adverse obstetric, maternal, and fetal outcomes, such as intrauterine death, premature delivery, postpartum hemorrhage, and neonatal deaths *(32)*. The exact patho-mechanism underlying this association remains poorly understood and may be related to several possible factors, such as differences in immune and hormonal changes occurring during pregnancy, and genetic and environmental factors *(32)*.

3.2.2. Burden of disease of HEV during pregnancy

Based on Rein et al. 2005 *(4)*, the probability of death given symptomatic illness differed substantially between non-pregnant and pregnant women. For non-pregnant women, the estimated probability of death given symptomatic illness was 0.019 (95% Cr.I.: 0.017-0.021) whereas for pregnant women, the model estimated a probability of death given symptomatic illness of 0.198 (95% Cr.I.: 0.169-0.227). HEV further accounted for 3,000 (95% Cr.I.: 1,892-4,424) stillbirths.

A systematic review and meta-analysis (Bigna et al. 2020) to estimate the global burden of HEV infection in pregnancy *(31)*, which included 52 studies (11,663 pregnant women), is suggestive of a high burden of HEV infection in pregnancy in high endemic countries, its association with poor materno-fetal outcomes and a high rate of vertical transmission. Infection with HEV increased the likelihood of maternal deaths (pooled odds ratio (OR): 7.17; 3.32–15.47).

In terms of maternofetal outcomes, HEV infection was associated with low birth weight (OR: 3.23; 1.71–6.10), small for gestational age (OR: 3.63; 1.25–10.49), preterm < 32 weeks (OR: 4.18; 1.23– 14.20), preterm < 37 weeks (OR: 3.45; 2.32–5.13), stillbirth (OR: 2.61; 1.64–4.14), intrauterine deaths (OR: 3.07; 2.13–4.43). No significant association with miscarriage (OR: 1.74; 0.77–3.90) was observed *(31)*.

Another systematic review (Bergløv et al. 2019) *(33)* which included 23 observational studies with a total of 1338 cases, estimated maternal case-fatality rate (CFR) to range from 3.2% (95% CI -0.4-6.9%) to 70% (95% CI 49.9-90.1%), with a median CFR of 26% (IQR 17-41%). In total, 12 studies reported fetal death (defined as an infant born with no signs of life at or after 20 weeks of gestation) and seven studies reported neonatal death. The fetal CFR ranged from 9.7% (95% CI 3.7; 15.7) to 61.9% (95% CI 52.6; 71.2),

with a median CFR of 33% (Interquartile range (IQR) 19%-37%). The neonatal CFR ranged from 2% (95% CI -0.2; 4.3) to 33.3% (95% CI 13.2; 53.5) with a median CFR of 8% (IQR 3%-20%) *(33)*.

Sensitivity analysis revealed that CFR did not change if calculated only for the 10 high-quality studies *(33)*.

Additional data collected during outbreaks, (not captured in Bigna *(31)* and Bergløv *(33)*) indicate an acute jaundice syndrome (AJS) case-fatality rate (CFR) of 10.4% among pregnant women in the context of a HEV outbreak (Clarke et al., 2013 South Sudan *(34)*). Likewise, in the context of an HEV outbreak in Uganda, CFR in AJS cases was 6.9% in pregnant women (Teshale et al.,2010 Uganda *(35)*). Boccia et al *(36)* investigated in hospitalized HEV cases a case-fatality ratio of 31.1% (19 of 61 women) and total of 18 deaths were recorded among jaundiced pregnant women (specific case-fatality ratio, 8.2%) with a camp setting in Darfur, Sudan *(36)*. In Namibia *(37)*, a retrospective cross-sectional study was performed between 2017-2019 including pregnant and postpartum women. ALF occurred in 28 (40.0%) of whom 13 died amounting to a case fatality rate of 18.6%.

3.2.3. Vaccine safety in pregnant women

In total, 4 studies contribute to the evidence-base on vaccination with HEV 239 during pregnancy:

- Safety of the hepatitis E vaccine for pregnant women: a preliminary analysis *(38)*.
- Safety of hepatitis E vaccination for pregnancy: a post-hoc analysis of a randomized, double-blind, controlled phase 3 clinical trial *(39)*.
- Cluster-randomized, blinded trial to assess the safety, immunogenicity and effectiveness of the hepatitis E vaccine HEV 239 (Hecolin®) in women of childbearing age in rural Bangladesh[1] (presentation provided to SAGE, available data to be presented during the SAGE meeting).
- Safety of hepatitis E vaccine in pregnancy: an emulated target trial following a mass reactive vaccination campaign in Bentiu IDP camp, South Sudan (in press; manuscript provided to SAGE and available data to be presented during the SAGE meeting).

Within the large phase 3 clinical trial of the recombinant hepatitis E vaccine (control hepatitis b vaccine), 37 of 31,791 women in the hepatitis E vaccine group and 31 of 31,735 women in the placebo (hepatitis B) group who were inadvertently vaccinated *(38)*. Nineteen (51.3%) of the women in the vaccine group and 14 (45.2%) in the placebo group underwent elective abortion. All infants were born without congenital anomalies. The weights, lengths, and gestational ages of the babies born to the mothers in the vaccine group and the control group, respectively, were comparable ($p > 0.05$). No spontaneous abortion occurred.

Within the phase 3 clinical trial of the HPV vaccine (control hepatitis E vaccine) *(39)*, the overall incidence of spontaneous abortion was 5.9% in the hepatitis E vaccine group and 6.4% in HPV group, ($p = 0.6056$). Incidence similar as the prevalence of spontaneous abortion in Chinese pregnant women described in other studies. The proximal exposure (vaccination during pregnancy or the onset of pregnancy within 90 days post any dose) Hepatitis E vaccination was not associated with a significantly higher risk of abnormal fetal loss than that of the HPV group (OR 0.80, 95% CI 0.38–1.70) as did distal

[1] Presentation at 2nd International Hepatitis E Symposium. 28-29 April 2023, related to cluster-randomized trial in women of childbearing age in rural Bangladesh. ICDDRB. ClinicalTrials.gov NCT02759991.

exposure (OR 1.02, 95% CI 0.76–1.37). Within the Hepatitis E vaccine group, no significant differences were noted between proximal and distal exposure in terms of abnormal fetal loss (OR 1.17, 95% CI 0.64–2.15), neonatal abnormality (OR 0.82, 95% CI 0.40–1.68) and pregnancy complications (OR 1.34, 95% CI 0.37–4.86). 66 women in hepatitis E vaccine group, 74 in HPV vaccine group were inadvertently vaccinated during pregnancy.

Within those inadvertently vaccinated, spontaneous abortions occurred in 4 women in each group, with no significant difference between the groups. Spontaneous abortions occurred in week 5/6/6/7 and week 5/6/13/17 for HPV group and HEV group, respectively (personal communication with manufacturer).

The GRADE and Evidence to Decision (E2D) assessments are shown in **Annex 3**.

Recent data from the pregnancy cohort in South Sudan as well as limited data from women inadvertently vaccinated during two phase 3 clinical trials *(38, 39)* were reassuring in terms of safety of HEV 239.

A presentation in April 2023 of blinded data[1] from the cluster-randomized, blinded trial to assess the safety, immunogenicity and effectiveness of the hepatitis E vaccine HEV 239 in women of childbearing age in rural Bangladesh identified a significant risk of spontaneous abortions in one group, exposure mainly around time of conception (0-3 weeks post conception). These data led GACVS to established a Working Group to assess these and other available data on HEV 239 administered during pregnancy. The group also considered indirect evidence from other (subunit) vaccines administered during pregnancy.

3.2.4. GACVS Working Group conclusions

The GACVS Working Group reviewed the available data from the two new studies (pregnancy cohort data from South Sudan and cluster-randomized trial data from Bangladesh) that evaluated the safety of the hepatitis E vaccine (Hecolin®) in pregnancy. The group also considered other data provided by the Hecolin® manufacturer (Innovax), as well as studies of safety outcomes for other protein subunit vaccines when administered shortly before or during pregnancy. The main conclusion from these deliberations is that, at this stage, a safety signal of spontaneous abortion associated with exposure to the Hecolin® vaccine in the 90-day period prior to pregnancy and during pregnancy derived from the large prospective cluster randomized trial in Bangladesh, cannot be disregarded. However, more analyses from the Bangladesh study could provide a better understanding of the observed risk for spontaneous abortion. This includes more precise data on the timing of vaccine exposure in relation to onset of pregnancy, the relationship with other vaccine-related adverse events and subgroup analyses to further explore participant-related risk factors. The Working Group concluded that it was unclear as to what potential biological or other mechanisms could be invoked to explain the risk seen in the Bangladesh trial, particularly given other protein subunit (non-live) vaccines have not been demonstrated to be associated with a risk of spontaneous abortion. Furthermore, the Working Group noted that consideration of the future use of hepatitis E vaccine by SAGE would need to consider the potential benefits of vaccination in a particular setting for potential use of the vaccine (e.g. in an outbreak setting); in such situations, strategies to avoid use prior to onset of or during early pregnancy could be employed, together with detailed analysis of safety outcomes. Further studies on the safety, immunogenicity and efficacy of the Hepatitis E vaccine administered in the second or third trimester of gestation and in women of childbearing age should be conducted to inform recommendations.

4. Selected planned and ongoing HEV vaccine-related research

A Phase II, randomized, placebo-controlled trial to evaluate the safety and immunogenicity of Hecolin® in pregnant women (second and third trimester) is planned to take place in Karachi, Pakistan *(40)*.

A total of 2,358 healthy pregnant and non-pregnant participants aged 16-45 years will be enrolled to receive 3 doses of Hecolin® (0,1 and 6 months). Primary objective is to evaluate the pregnancy related safety events (pregnancy-related Adverse Event of Special Interest (AESI)) and Serious Adverse Event (SAE) among pregnant recipients of 2 doses of Hecolin® administered 4 weeks apart compared to placebo recipients. Further, objective is to demonstrate immune non-inferiority of pregnant recipients compared to non-pregnant recipients of 2 doses of Hecolin® as measured by the geometric mean concentration (GMC) of anti-HEV IgG at 4 weeks following the second dose. This trial is currently on hold as the funder (Bill & Melinda Gates Foundation) is awaiting the GACVS and SAGE recommendation.

In addition, a phase 2b, open label study to evaluate immunogenicity and safety of Hecolin® in HIV positive adult participants followed by randomized, observer-blind, placebo-controlled study to evaluate the immunogenicity and safety of Hecolin® in children has been initiated in South Africa.

5. Draft recommendations

1. SAGE reiterates the importance of hepatitis E as a public health problem in many low and middle income countries. The risk of severe disease is particularly high in individuals with certain underlying conditions such as pregnant women and those with pre-existing liver disease or immunosuppression. The risk of exposure is particularly high in certain fragile and conflict-affected areas lacking adequate WASH, with endemic or epidemic disease transmission patterns. In these settings, limited or missing access to supportive care further increases the risk of severe disease outcomes, in particular in vulnerable population groups such as pregnant women.
2. To this end, SAGE re-emphasizes the importance of HEV vaccination in special situations such as outbreaks and fragile and conflict affected settings where individuals are considered at high risk of exposure and severe disease.
3. In settings with documented HEV circulation, the risk-benefit of vaccinating women during pregnancy, in particular during the second and third trimester, outweighs the potential harms.
4. The possible risk of spontaneous abortion identified by one trial following HEV vaccination around the time of conception and very early pregnancy needs further assessment. In the meantime, it should not deprive women of childbearing age or pregnant women of a potentially life-saving intervention when the epidemiological situation suggest a high risk of exposure. As for all vaccines, informed consent remains paramount. This should include providing women of childbearing age with relevant information on potential risks.
5. SAGE highlights the importance of vaccination in mitigating the impact of hepatitis E and promoting equity since hepatitis E disproportionately affects underprivileged populations in low-resource settings. Based on local epidemiology, countries may consider HEV vaccination in a geographically confined areas (e.g. IDP camp) with documented sporadic or endemic HEV circulation and high risk of exacerbation of HEV cases (e.g. due to contextual factors).
6. When implementing vaccination in fragile and conflict affected settings and outbreaks, using a 2 dose schedule (0 and 1 month) may be considered.
7. SAGE welcomes the recent approval of HEV as a vaccine stockpiled under the ICG as a solution to one important barrier to vaccine access and, once in place, encourages countries to obtain vaccines via this mechanism.
8. SAGE underlines the importance of generating additional evidence to allow more robust policy recommendations on HEV vaccination, in particular on safety in pregnant women and in other population groups such as children and immunocompromised individuals. Wherever vaccine campaigns are implemented, SAGE stresses the importance of accompanying HEV use with public health research whenever possible.
9. SAGE welcomes the planned trials on vaccination during pregnancy in Pakistan and in people living with HIV and in individuals under 16 years of age in South Africa and asks to be informed on the outcomes of these trials.
10. More robust data are further required on burden of disease, including on the burden and role of children in transmission, to inform optimal vaccination strategies.
11. SAGE notes the pivotal role of improved surveillance and access to diagnostics to detect hepatitis E outbreaks so as to allow a timely response.

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7. Annexes

Annex 1: List of studies excluded from the final review

Author, year; location	Brief description	Type of data included	Reason for exclusion
During initial vaccine development			
Zhang *et al*, 2005; China	Phase I study	Safety	No data on immunogenicity / efficacy
Wu et al, 2012; China	Subset analysis of women who inadvertently received either HEV 239 (n=37) or hepatitis B vaccine (n=31) in the phase III trial (Zhu *et al*, 2010; China)	Safety	No data on immunogenicity / efficacy of HEV 239
Wu *et al*, 2013; China	Subset analysis of 14,065 participants with known HBsAg status at baseline in the Phase III trial (Zhu *et al*, 2010; China)	Safety and immunogenicity	No data on immunogenicity after one or two doses of HEV 239. Individuals with fewer than three doses were excluded from analysis.
Post-licensure studies			
Yu *et al*, 2019; China	Open labelled controlled trial in elderly participants (>65 y) using 3 dose usual schedule (0,1 and 6 mo)	Safety and immunogenicity	No data on immunogenicity were available after one or two doses of HEV 239. Individuals with less than three doses were excluded from analysis.
Zhao *et al*, 2022; China	Double blind trial, with participants randomised to receive 3 doses of either bivalent HPV 16 and 18 or HEV 239 (placebo) at 0,1 and 6 months	Safety and efficacy	Efficacy to prevent high-grade genital lesions by HPV 16 and 18 was noted. No data on efficacy to prevent hepatitis E (either serological or clinical infection)
Unpublished: Clinicaltrials.gov ID NCT02584543; China	Coadministration of HEV 239 with hepatitis B vaccine	Safety and immunogenicity	No data on immunogenicity after one or two doses of HEV 239. Individuals with fewer than three doses were excluded from analysis.
Unpublished: Clinicaltrials.gov ID NCT03365921; China	HEV 239 lot-to-lot consistency	Safety and immunogenicity	No data on immunogenicity after one or two doses of HEV 239. Individuals with fewer than three doses were excluded from analysis.

Annex 2: GRADE and E2D on the use of a 2-dose schedule

GRADE table: Two dose schedule

Does administration of less than a full schedule (2 doses at month 0 and 1) compared to no vaccination/ placebo/ the full schedule in individuals over 16 years of age confer protection against HEV?				
			Rating	Adjustment to rating
Certainty Assessment	No of studies[2]/starting rating		1/ RCT *(15)*	4
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	None serious[3]	0
		Publication bias	None serious	0
	Factors increasing confidence	Strength of association	Not applicable	0
		Dose-response	Not applicable	0
		Mitigated bias and confounding	Not applicable	0
	Final numerical rating of certainty of evidence			**4**
Summary of Findings	**Statement on certainty of evidence**			Evidence supports a high level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome.
	Conclusion			We are very confident that a 2 dose series (0, 1 month) of Hepatitis E vaccine confers high levels of clinical protection against Hepatitis E disease up to 30 months following immunization.

[2] During the time period between 1.5 months to 30 months (beginning 15 days after the second dose), six cases of acute hepatitis E were recorded among placebo recipients (n=3765 between 6 months to 30 months, and n=52,428 till administration of the third dose) and none among the HEV 239 vaccine recipients (n=3542 between 6 months to 30 months, and n=52,235 till administration of third dose), indicating an efficacy of 100.0% (95%CI: 15.4% to 100.0%)

[3] Albeit wide confidence intervals, no downgrading due to supportive evidence demonstrating a strong anti-HEV antibody response that remained detectable for at least two years.

Evidence to Decision table: Two dose schedule

Question: **In individuals in outbreaks, fragile and conflict-affected settings, is administration of less than a full schedule (0,1 and 6 months) a possible alternative to confer protection against HEV?**

Population: **Individuals in the context of a HEV outbreak occurring in a fragile and/or conflict-affected settings**

Intervention: **Less than a full schedule (2 doses at month 0 and 1)**

Comparison(s): **No vaccination/ placebo/ full schedule (0,1 and 6 months)**

Outcome: **HEV disease**

Background: Hepatitis E outbreaks particularly occur in overcrowded, low-income settings with inadequate access to clean water and disposal of human feces. Those living in fragile, conflict-affected settings and vulnerable populations, especially refugees or internally displaced persons (IDP) are disproportionally affected. The three-dose regimen of HEV 239 vaccine is known to induce a strong antibody response, which has been shown to be protective for at least 10 years. However, the schedule of administration is quite prolonged, making its implementation challenging in situations where quick protection is desired or in settings with frequent population movement.

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies by setting* ☐	HEV represents a significant public health problem. A recent systematic review *(6)* identified 44 HEV outbreaks in 19 countries. Most of the outbreaks occurred in Africa (n = 27, 61.4%) and Southeast Asia (n = 12, 27.3%) regions. Humanitarian settings (e.g., camp settings such as refugee camps and internally displaced person settlements) were the most common places (n = 12, 27.3%) where HEV outbreaks were identified. The review further concluded significant under-reporting of HEV outbreaks.	
BENEFITS & HARMS OF THE OPTIONS	<u>Benefits of the intervention</u> Are the desirable anticipated effects large?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies* ☐	The two-dose (0 and 1 month) schedule showed rapid and strong antibody response that remained detectable for at least a year (see review page 5). Durable and a protective antibody response was noted irrespective of the number of HEV 239 vaccine doses administered in participants who were seropositive for anti-HEV antibodies at baseline. In baseline seronegative participants, even-though only marginal antibody levels were	

				detected at prolonged follow-up after two-doses of HEV 239, the antibody levels were comparable to those in three-dose schedule at 13 months of follow-up; which could be useful in outbreak control situations. Efficacy of two-dose HEV 239 to prevent hepatitis E was comparable to three-dose schedule in the short term.	
	<u>Harms of the intervention</u> Are the undesirable anticipated effects small?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies* ☐	In general, HEV 239 is well tolerated and specific safety concerns were observed neither following dose 2 nor following dose 3 in the safety subset of the large phase 3 clinical trial *(12)*. It remains to be assessed whether a reduced schedule infers equal long-term protection, though at 4.5 years follow-up in those having received at least one dose, vaccine efficacy remained at 85% (95% CI: 67.1-93.3%)*(14)*.	
	Balance between benefits and harms	*Favours inter-vention* ☐	*Favours com-parison* ☐	*Favours both* ☒	*Favours neither* ☐	*Unclear* ☐	Balancing benefits and harms, at least in the short-term, evidence suggests that a two dose schedule at 0 and 1 month elicits protection comparable to the full schedule.	
	What is the overall certainty of this evidence for the critical outcomes?	*Efficacy of the intervention* *No included studies* ☐	*Very low* ☐	*Low* ☐	*Mod-erate* ☐	*High* ☒	We are very confident that a 2 dose series of Hepatitis E vaccine confers high levels of clinical protection against Hepatitis E disease up to 30 months following immunization. Safety following 2 doses hasn't been evaluated in the context of this review, though previous certainty assessments concluded that evidence supports a moderate degree of confidence in the estimate of the effect that incidence of serious adverse events following any dose of hepatitis E vaccination is low. Judged on the phase I, II and III trials and the reactogenicity subset of the latter study, the rates of solicited adverse events were not concerning.	
		Safety of the intervention *No included studies* ☒	*Very low* ☐	*Low* ☐	*Mod-erate* ☐	*High* ☐		
V AL		*Important*	*Possibly*	*Probably no*	*No impor*	*No known*	No scientific evidence is available on the relative importance that the target population attributes	

	How certain is the relative importance of the desirable and undesirable outcomes?	*uncertainty or variability* ☐	*important uncertainty or variability* ☒	*important uncertainty or variability* ☐	*important uncertainty or variability* ☐	*undesirable outcomes* ☐	to the desirable outcomes and undesirable outcomes. Different population groups may have different opinions regarding the weights assigned to the desirable and undesirable outcomes. It is assumed that there is possibly important uncertainty regarding the relative importance.	
	Values and preferences of the target population: Are the desirable effects large relative to undesirable effects?	*No* ☐	*Probably No* ☐	*Uncertain* ☐	*Probably Yes* ☒	*Yes* ☐	*Varies* ☐	No scientific evidence on the relative importance of the desirable and undesirable effects of intervention. Different population groups may have different values and preferences regarding the weights assigned to the desirable and undesirable effects of the intervention. That said, the desirable effects of the interventions is probably seen as large compared to the undesirable effects.	
RESOURCE USE	Are the resources required small?	*No* ☐	*Uncertain* ☐		*Yes* ☒		*Varies* ☐	In general, additional resources are required for implementation of the intervention and the comparison, though the resources for implementation of the intervention are assumed to be smaller than for implementation of the comparison given the administration of fewer vaccine doses.	
	Cost-effectiveness	*No* ☐	*Uncertain* ☐		*Yes* ☒		*Varies* ☐	No formal cost-effectiveness analysis have been conducted on these settings, but the it is assumed that for inducing immediate, at least short-term protection, implementation of a reduced schedule is the more cost-effective option.	
EQUITY	What would be the impact on health inequities?	*Increased* ☐	*Uncertain* ☐		*Reduced* ☒		*Varies* ☐	Equity and ethical considerations are critical. In the context of an HEV outbreak, particularly in hard-to reach or otherwise already disadvantaged communities, implementation of this preventive intervention would reduce health	

			inequities as these communities often lack access to WASH and symptomatic treatment.	
ACCEPTABILITY	Which option is acceptable to key stakeholders (Ministries of Health, Immunization Managers)?	*Inter-vention* ☒ / *Com parison* ☐ / *Both* ☐ / *Neither* ☐ / *Un-clear* ☐	Vaccination is an important tool to combat HEV and key stakeholders, in particular ministries of health and immunization managers, are assumed to be in favour of administration of less than full HEV vaccination schedule due to ease of implementation and reduced costs.	
	Which option is acceptable to target group?	*Inter-vention* ☒ / *Com parison* ☐ / *Both* ☐ / *Neither* ☐ / *Un-clear* ☐	HEV vaccine acceptability may vary between (sub)populations and may be correlated with the perceived risk posed by the disease. The intervention would likely be preferred due to the reduced dosing scheme.	
FEASIBILITY	Is the intervention feasible to implement?	*No* ☐ / *Probably No* ☐ / *Uncertain* ☐ / *Probably Yes* ☐ / *Yes* ☒ / *Varies* ☐	Administration of the HEV vaccine in these settings may pose a challenges, though the intervention has clear advantages over the comparison as it allows for more rapid protection in settings with high population movement.	

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences *is closely balanced or uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings
	☐	☐	☐	☐	☒

Type of recommendation	We recommend the intervention ☒	We suggest considering recommendation of the intervention ☐ Only in the context of rigorous research ☐ Only with targeted monitoring and evaluation ☐ Only in specific contexts or specific (sub)populations	We recommend the comparison ☐	We recommend against the intervention and the comparison ☐
Recommendation (text)	Please see draft recommendations page 21.			
Implementation considerations	Please see draft recommendations page 21.			
Monitoring and evaluation	Please see draft recommendations page 21.			
Research priorities	Please see draft recommendations page 21.			

Annex 3 : GRADE and E2D on vaccination during pregnancy

GRADE table: Pregnancy

What is the risk of adverse maternofetal outcome after vaccination of pregnant women with HEV compared to no vaccination/ placebo.				
			Rating	Adjustment to rating
Certainty Assessment	No of studies/starting rating		2/ RCT *(38, 39)*[4]	4
	Factors decreasing confidence	Limitation in study design[5]	Serious	-1
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision[6]	Serious	-2
		Publication bias	None serious	0
	Factors increasing confidence	Strength of association	Not applicable	0
		Dose-response	Not applicable	0
		Mitigated bias and confounding	Not applicable	0
	Final numerical rating of certainty of evidence			**1**
Summary of Findings	**Statement on certainty of evidence**			Evidence supports a very low level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome.
	Conclusion			Sample size was too small to conclude on the true effect estimate.

[4] The additional studies will be taken into consideration in the certainty assessment of the body of evidence once the data are publicly available.
[5] Safety of vaccination during pregnancy was not the outcome measures. Pregnant women were excluded from the trial, analysis are based on a post-hoc assessment in women inadvertently vaccinated during pregnancy.
[6] Very small sample size, 37 women (Wu et al. 2012) and 66 women (Zhang et al. 2023) in hepatitis E vaccine groups were inadvertently vaccinated during pregnancy.

Evidence to Decision table: Pregnancy

Question: **Should pregnant women in the context of outbreaks and fragile and conflict affected settings be vaccinated against HEV.**
Population: **Pregnant women in the context of a HEV outbreak occurring in a fragile and/or conflict-affected settings**
Intervention: **Vaccination against HEV**
Comparison(s): **No vaccination**
Outcome: **Severe HEV-related maternal, fetal and neonatal outcomes**

Background: Pregnant women, in particular in the second or third trimester of gestation, are at a greater risk for development of symptomatic disease than are non-pregnant women and men and carry a greater risk for progression to ALF, as compared with nonpregnant persons with hepatitis E. HEV infection in pregnancy is also associated with an increased risk for adverse obstetric, maternal, and fetal outcomes, such as intrauterine death, premature delivery, postpartum hemorrhage, and neonatal deaths.

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies by setting* ☐	The probability of death given symptomatic illness differed substantially between non-pregnant and pregnant women *(4)*. A systematic review and meta-analysis (to estimate the global burden of HEV infection in pregnancy *(31)* is suggestive of a high burden of HEV infection in pregnancy in high endemic countries, its association with poor materno-fetal outcomes, and a high rate of vertical transmission. Infection with HEV increased the likelihood of maternal deaths (pooled odds ratio (OR): 7.17; 3.32–15.47).	
BENEFITS & HARMS OF THE OPTIONS	<u>Benefits of the intervention</u> Are the desirable anticipated effects large?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies* ☐	In individuals ≥16 years of age, HEV 239 is highly efficacious and well tolerated *(12)*. While data on vaccination during pregnancy are limited, there is currently no evidence suggesting that the vaccine is less protective in pregnant women.	

	Harms of the intervention Are the undesirable anticipated effects small?	*No* ☐ | *Un-certain* ☐ | *Yes* ☒ | *Varies* ☐	Regarding the safety of Hepatitis E vaccine in pregnant women, limited data show (37 pregnant women inadvertently vaccinated during the Phase III trial) that the vaccine was well tolerated in pregnant women with rates of adverse events similar to those observed in matched non-pregnant women. Hepatitis E vaccine was further used as comparator vaccine in HPV trial, about 1000 women in the Hepatitis E group became pregnant in the course of the trial. No serious adverse events were reported. Data from vaccine use in South Sudan indicate that it is well tolerated in pregnant women Data from a cluster-randomized trial in Bangladesh in women of childbearing age indicate an increased risk of spontaneous abortions in a post-hoc analysis.	
	Balance between benefits and harms	*Favours inter-vention* ☒ | *Favours com-parison* ☐ | *Favours both* ☐ | *Favours neither* ☐ | Unclear ☐	While more data are needed, the benefits and harms need to be assessed in the context of the epidemiological situation. The benefits of the intervention likely outweigh the potential harms in the context of HEV outbreak occurring in a fragile and/or conflict-affected settings, where pregnant women are at high risk of exposure.	
	What is the overall certainty of this evidence for the critical outcomes?	*Effectiveness of the intervention* ***No included studies*** ☒ | ***Very low*** ☐ | ***Low*** ☐ | ***Mod-erate*** ☐ | ***High*** ☐ *Safety of the intervention* ***No included studies*** ☐ | ***Very low*** ☒ | ***Low*** ☐ | ***Mod-erate*** ☐ | ***High*** ☐	Sample size was too small to conclude on the true effect estimate of the risk of maternofetal outcomes after vaccination of pregnant women with HEV vaccine. Vaccine efficacy in pregnant women has not been evaluated in the context of this review, though the certainty of evidence in the general population of a previous certainty assessment concluded that evidence supports a moderate degree of confidence in the estimate of the effect.	
VALUES &	How certain is the relative importance of the desirable	*Important uncertainty or* | *Possibly important uncer* | *Probably no important uncer* | *No important uncertainty* | *No known undesirable*	No scientific evidence is available on the relative importance that the target population attributes to the desirable outcomes and undesirable outcomes. Different population groups may	

	and undesirable outcomes?	*varia bility* ☐	*tainty or varia bility* ☐	*tainty or varia bility* ☒	*or varia bility* ☐	*outco mes* ☐	have different opinions regarding the weights assigned to the desirable and undesirable outcomes, though it is assumed that there is probably no important uncertainty regarding the relative importance of the desirable and undesirable outcomes.	
	Values and preferences of the target population: Are the desirable effects large relative to undesirable effects?	*No* ☐	*Pro babl y No* ☐	*Unc erta in* ☐	*Pro babl y Yes* ☒	*Ye s* ☐	*Varie s* ☐	No scientific evidence on the relative importance of the desirable and undesirable effects of intervention. Different population groups may have different opinions regarding the weights assigned to the desirable and undesirable effects of the intervention. That said, the desirable effects of the interventions is probably large compared to the undesirable effects.	
RESOURCE USE	Are the resources required small?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies* ☐		In general, additional resources are required for implementation of HEV vaccination in the context of an outbreak, though vaccine is accessible to countries at no cost through the ICG stockpile.	
	Cost-effectiveness	*No* ☐	*Un-certain* ☒	*Yes* ☐	*Varies* ☐		No formal cost-effectiveness analysis have been conducted on vaccination of pregnant women in these settings.	
EQ		*Increa-sed*	*Un-certain*	*Re-duced*	*Varies*		Equity and ethical considerations	

	What would be the impact on health inequities?	☐ ☐ ☒ ☐	are critical. In the context of a HEV outbreak, particularly in high-risk groups such as pregnant women in hard-to reach or otherwise already disadvantaged communities, implementation of the intervention would reduce health inequities and address gender-related health inequality.	
ACCEPTABILITY	Which option is acceptable to key stakeholders (Ministries of Health, Immunization Managers)?	*Inter-vention* ☒ / *Com parison* ☐ / *Both* ☐ / *Neither* ☐ / *Un-clear* ☐	Vaccination is an important tool to combat HEV and key stakeholders, in particular ministries of health and immunization managers, are assumed to be in favour of administration vaccination to protect this vulnerable population group.	
	Which option is acceptable to target group?	*Inter-vention* ☒ / *Com parison* ☐ / *Both* ☐ / *Neither* ☐ / *Un-clear* ☐	No scientific evidence is available. HEV vaccine acceptability may vary between population groups. For pregnant women, acceptability may be correlated with the perceived risk posed by the disease versus any potential adverse intervention-related outcomes.	
FEASIBILITY	Is the intervention feasible to implement?	*No* ☐ / *Probably No* ☐ / *Uncertain* ☐ / *Probably Yes* ☐ / *Yes* ☒ / *Varies* ☐	Administration of the HEV vaccine may pose a challenges, dependent on the setting, though large, successful HEV campaigns have been launched and implemented, targeting also in pregnant women.	

Balance of consequences				
Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences *is closely balanced or uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings

	☐	☐	☐	☒	☐
Type of recommendation	We recommend the intervention ☐	We suggest considering recommendation of the intervention ☐ Only in the context of rigorous research ☒ Only with targeted monitoring and evaluation ☐ Only in specific contexts or specific (sub)populations		We recommend the comparison ☐	We recommend against the intervention and the comparison ☐
Recommendation (text)	Please see draft recommendations page 21.				
Implementation considerations	Please see draft recommendations page 21.				
Monitoring and evaluation	Please see draft recommendations page 21.				
Research priorities	Please see draft recommendations page 21.				