WHO/UNICEF Zika Virus (ZIKV) Vaccine Target Product Profile (TPP):
Vaccine to protect against congenital Zika syndrome for use during an emergency

Updated February 2017

The purpose of this document:

This TPP describes the preferred and minimal product characteristics for vaccines aimed at protecting against congenital ZIKV syndrome during emergency situations, such as the current or a future ZIKV outbreak. With that public health objective, this TPP is primarily aimed at vaccines for use in women of repoductive age, which may include pregnant women, with adolescent and adult males as a secondary target population if resources permit. The TPP has been drafted by a WHO working group of subject matter experts with diverse areas of expertise. It has undergone public consultation, and discussion in various fora. As our understanding of Zika epidemiology and pathology evolves rapidly, the TPP should be considered a living document. The first version was published in July 2016, and this revision incorporates considerations based on new data that has emerged in the last 6 months. It will continue to be adapted as knowledge on ZIKV evolves.

While this document contains assumptions with respect to regulatory considerations, in order to help frame the rationale for the proposed characteristics*, this TPP should not be considered as a regulatory document.* A separate consultation was held in June 2016 to discuss regulatory considerations for a vaccine with the characteristics described in this document.[1]

This document is intended to inform vaccine developers, regulatory agencies, procurement agencies and funders on vaccine research and public health priorities, and to facilitate the most expeditious development of vaccine candidates that address the greatest and most urgent public health need. It will inform subsequent development of WHO policy recommendations for use, and provide the framework of the WHO Emergency Use Assessment Listing (EUAL) for ZIKV vaccines, if relevant.[2] Countries may consider emergency use or conditional approval regulatory pathways for ZIKV vaccine registration according to their national legislation. It may also serve as basis for the formulation of advance purchase commitments.

Background:

Although the recent Public Health Emergency of International Concern (PHEIC) was declared over by the WHO Director-General on 18 November 2016, ZIKV remains an enduring public health challenge requiring intense action.[3] There are likely to continue to be outbreaks that put susceptible populations at risk. This TPP prioritizes prophylactic vaccination as a strategy to prevent prenatal ZIKV infection resulting in microcephaly, other nervous system malformations and pregnancy-related complications, in line with the WHO Zika Strategic Response plan.[4] Therefore, the immunization of women of reproductive age, which may

include pregnant women, is considered to be of highest priority. This population is prioritized based on available evidence that has accumulated to infer a causal relationship between prenatal ZIKV infection and microcephaly, and other severe brain anomalies.[5] It is plausible, based on other maternal-fetal vaccination outcomes data (e.g. rubella), that effective immunization of women of reproductive age may protect the foetus from infection or prevent or attenuate the congenital abnormalities associated with infection. In addition to vulnerability during the first trimester, evidence is accumulating that ZIKV infection in the 2nd and 3rd trimesters can also lead to adverse fetal and post-natal outcomes. It is an individual and public health priority to protect women throughout their pregnancy. Since males contribute to disease transmission and represent an important target population, they would be vaccinated in addition to women of reproductive age in an emergency context, providing vaccine supply and resources are available to do so.

At least two scenarios can be envisaged for a ZIKV vaccine for which WHO SAGE would advise on immunization strategies:

A. **Outbreak response:** In the context of an ongoing epidemic or an imminent outbreak of ZIKV, a mass vaccination campaign will help to prevent ZIKV-associated disease in women of reproductive age. Subject to risk-benefit assessment, pregnant women may also be an important target group. The primary public health objective of vaccination in this scenario is the prevention of prenatal ZIKV infection, associated microcephaly, other nervous system malformations and pregnancy-related complications. Other populations, in particular men, may be included in emergency vaccination campaigns, if vaccine supply permits.

B. **Routine/endemic transmission use:** During an inter-epidemic period, a broad-based or universal vaccination campaign of the general population, extending from early childhood to adults, followed by routine immunization, is a possible scenario The extend of the catch-up will depend on the epidemiological situation, and may include adult populations. The primary public health objective of vaccination in this scenario, in addition to prevention of ZIKV-associated illness and prenatal ZIKV infection during a subsequent outbreak, is to establish population immunity.

This TPP is oriented towards addressing Scenario A, the outbreak response. Although the epidemiology of ZIKV in the aftermath of large epidemics such as has occurred in Latin America is currently unknown, there are likely to continue to be outbreaks in the coming years in populations with low immunity. Such outbreaks could occur in Latin America or other parts of the world, such as Asia and Africa. Thus, Scenario A continues to be relevant. While a vaccine for Scenario B is desirable, current data on the epidemiology of ZIKV outside the context of large epidemics are insufficiently understood for the development of a TPP at this time. As our understanding of global ZIKV transmission in the aftermath of large epidemics improves, it is anticipated that a TPP for Scenario B may be warranted. Notably, some vaccine products may address both scenarios.

The primary objective in the emergency/outbreak context will be prevention of congenital ZIKV syndrome through the protection of pregnant women through the duration of their pregnancy.

At the time of drafting this updated ZIKV vaccine TPP, several key features of ZIKV epidemiology and pathology remain incompletely understood, some of which are highlighted below:

- Despite an apparent low case fatality rate,[6,7,8] ZIKV infection is associated with a spectrum of clinical disease which can be severe, most notably congenital neurological abnormalities and other rare CNS pathologies, as well Guillain-Barré Syndrome (GBS).[9,10,11] The full range of clinical and developmental consequences of infection during pregnancy is still under investigation,[12] and the relationship between viraemia level/duration and fetal pathology is incompletely understood. Furthermore, the rates of microcephaly have varied by country/region,[13,14,15] and the causes for this, including potential cofactors that may enhance risk of microcephaly, are currently not well understood.
- It is well accepted that ZIKV infection is associated and likely to be causally related to GBS.[16,17,18] Elicitation of autoimmune responses by ZIKV infection (e.g. anti-ganglioside antibodies), has been postulated to play a role in the increased incidence of neurological complications,[19] but a direct viral effect cannot currently be excluded either given some evidence of the close temporal proximity between signs of ZIKV disease and onset of GBS-like symptoms.[17,10]
- Many cases of ZIKV infection are asymptomatic, and the mechanisms leading to asymptomatic vs. symptomatic infection, as well as the pathogenic mechanisms for progression to severe disease, are not well understood.
- Currently, the relationship between viraemia, symptomatic disease, and fetal abnormality in humans is not well characterised. Thus, it is uncertain whether a vaccine that prevents clinical disease in a vaccinated woman would be sufficient to prevent viral transmission to the fetus. It is assumed that reduction in ZIKV illness incidence is associated with a reduction in ZIKV viraemia, which in turn will reduce the risk of, or prevent fetal ZIKV infection and the subsequent development of congenital anomalies. While it has been suggested that fetal brain abnormalities occur more frequently when the mother had more pronounced ZIKV illness, the risk of asymptomatic infection of pregnant women leading to congenital ZIKV syndrome is not well understood. In one study in Salvador, Brazil, approximately 35% of women who gave birth to an infant with microcephaly recalled experiencing ZIKV-like symptoms.[20] Available data suggest that infection during the first trimester of pregnancy is more strongly associated with microcephaly in the neonates;[21,22] however, there is growing evidence that infection in the 2nd and 3rd trimesters causes congenital brain injury,[23,24] potentially at similar rates across the pregnancy.[20] The effects of ZIKV infection during the perinatal period are incompletely understood.
- Promising data using mouse and non-human primate (NHP) models showing immunogenicity and protection against viraemia from ZIKV challenge have been published,[25,26] and work is actively ongoing to develop models that could be used to demonstrate vaccine prevention of associated pathologies such as microcephaly and GBS.[27,28]
- It is currently unknown whether previous infection with or vaccination against other flaviviruses might impact the severity of ZIKV disease or vice versa. The role of potentially cross-reactive antibodies in disease prevention or enhancement is still unclear. Several *in vitro* studies have demonstrated both,[29,30,31,32] but the generalization of such studies to the human immunological experience and its clinical relevance is not possible. Preliminary data in flavivirus-primed NHP do not show any signs of enhanced disease.[33] Nevertheless, it is an important area for further field evaluation.
- While there are currently no established guidelines regarding testing of new vaccines in a population that is likely to include pregnant women, the US Food and

Drug Administration (FDA) recently convened the Vaccines and Related Biological Products Advisory Committee (VRBPAC), in order to discuss the appropriate clinical study designs to support the safety and effectiveness of investigational vaccines, as well as included study designs of licensed vaccines that are recommended for use in pregnancy to protect the infant.[34,35]

- In the context of a highly epidemic disease (e.g. epidemic period <1 year) with an apparent short duration of detectable viraemia and relatively infrequent incidence of clinical disease, it may be difficult to generate clinical efficacy data in a feasible sample size and an acceptable timeframe. The degree of post-epidemic virus circulation is currently not known. In the coming months the feasibility of efficacy evaluation in affected areas will need to be reassessed, and alternate clinical development strategies may be required.
- This TPP thus focuses on direct protection in this target population; however, it is recognized that there are currently important unknowns about the potential effects of ZIKV disease in males as well as the role of sexual transmission. A study was recently published suggesting ZIKV infection in mice causes tissue damage to testes and potential infertility.[36] ZIKV as measured by RT-PCR has been measured in semen up to over 180 days post infection[37] and sexual transmission has been observed to occur 34 to 41 days after the index case.[38] Some epidemiological data have suggested a higher incidence rate of ZIKV disease in females,[39,40,41] potentially due to higher sexual transmission from males to females; however, this is only one of a number of potential hypotheses. Both the potential consequences of ZIKV infection in males and the role of sexual transmission in the burden of ZIKV require further study to inform the prioritization of males as a target population for vaccination.
- Given the rarity of congenital Zika syndrome and GBS, the evaluation of vaccine effectiveness against these outcomes is expected to be evaluated in post-authorization studies.
- The potential impact of a ZIKV vaccine on virus transmission by different routes needs to be considered once a better understanding of the epidemiology of the disease has been obtained.

Demonstration of prevention of ZIKV infection and/or disease in an established animal model(s) is anticipated to be desirable. It is also assumed that data on induction of a defined threshold of antibodies are reasonably likely to predict clinical benefit, as is the case for other flaviviruses. Correlates of protection have been defined for TBE,[42] YF[43] and JE[44] vaccines. The establishment of a surrogate or correlate of protection could lower the need to obtain clinical efficacy data pre-licensure.

At the present time (2017), while efforts focus on outbreak/emergency response, vaccine development may appropriately prioritize monovalent (single-organism) ZIKV vaccines.

Structure of this document:

The document defines product characteristics and proposes preferred and minimal criteria for each characteristic. Explanatory notes are provided on the rationale and assumptions made in developing the characteristics and criteria.

Where appropriate, the document stratifies considerations by vaccine platform, since it is anticipated that the characterisation and safety requirements for live attenuated or replication competent viral vaccines in women of reproductive potential are likely to be more stringent than for single-cycle replication defective vectors and non-replicating vaccine

platforms, such as inactivated whole or split virus-, or nucleic acid- or subunit protein-based vaccine candidates. The latter technologies are likely to be more acceptable for use in pregnant women, be it off-label or through an indication.

None of the characteristics in the tables below dominates over any other. Therefore should a vaccine's profile be sufficiently superior to the minimal characteristics under one or more categories, this may outweigh deficiencies in meeting another specific minimal characteristic.

The following subject matter experts were consulted on various aspects during preparation of this and/or previous versions of the TPP: Alan Barrett (University of Texas Medical Branch), Klaus Cichutek (PEI), Alejandro Cravioto (Global Evaluative Sciences, Inc.), Eric D'Ortenzio (INSERM), Anna Durbin (John Hopkins School of Public Health), David Kaslow (PATH), Heidi Meyer (PEI), Ted Tsai (Takeda Vaccines), Stephen Thomas (State University of New York Upstate Medical University), Doug Wassenaar (SARETI, University of Kwazulu-Natal), and representation from US Government. The document was also endorsed by members of the PDVAC committee: http://www.who.int/immunization/research/committees/pdvac/en/.

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Vaccine characteristic	TPP for Emergency use		Product development considerations and assumptions
	Preferred	**Minimal**	
Indication for use	For the prevention of Zika virus-associated clinical illness of any severity in subjects 9 years of age or older		Prevention of clinical illness has been selected as the indication for use. The prevention of ZIKV infection (sterilising immunity) would be an alternative, but might be difficult to achieve based on experience with other flavivirus vaccines, such as YF, TBE, and JE.[42,43,44] Alternatively or in addition to prevention of clinical disease, the prevention of infection could be estimated by measuring the absence of viraemia in urine or saliva or the absence of seroconversion (or anamnestic response) post-vaccination with specific serologic tests. The assumption is that a reduction in viraemia below a threshold will prevent/reduce clinical illness, and prevent infection of the foetus and possibly placenta, thereby resulting in prevention of congenital abnormalities. While it is hoped that preclinical models will support this assumption, it will have to be validated through effectiveness studies. Clinical illness refers to a virologically-confirmed case of ZIKV illness as defined by WHO/PAHO.[45] If prevention of clinical illness, and possibly infection, is not feasible to assess in a controlled clinical trial during the current outbreak, it will need to be studied post-authorization. It is assumed that effectiveness against the longer term sequelae of GBS and congenital ZIKV syndrome will only be possible to assess post-authorization. It is not expected that initial products would contain an indication for use in pregnant women at the outset. This may be sought at a later

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			stage following dedicated clinical studies in pregnant women. It is advisable that developers generate data on safety in pregnant women. It should be noted that many vaccines routinely used in pregnancy do not have a specific indication for use in pregnancy, and that the lack of an indication should not preclude the use of a safe and effective vaccine in pregnancy, especially in the context of an epidemic or imminent outbreak.
Contra-Indication	No contraindication for use during pregnancy or in lactating women		Theoretical risk may not preclude the exceptional use during pregnancy or in lactating women during an outbreak. Immunization advisory groups may recommend vaccination of pregnant women with due consideration of risks and benefits, and women who are unknowingly pregnant may be vaccinated, as screening with pregnancy tests is considered infeasible during an emergency campaign.
Target population	Women of reproductive age (including adolescent and pre-adolescent girls 9 years of age or older), and boys/men of the same ages. Potential exclusions: pre-existing neurologic or autoimmune disorders, immuno-suppressed individuals, depending on the vaccine platform used.		In an emergency use context, vaccination would be prioritized to women of reproductive age, which may include pregnant women, as this group is considered at high risk due to the causal relationship between prenatal ZIKV infection and microcephaly, other nervous system malformations and pregnancy-related complications. Mass vaccination of this target population could potentially also mitigate against sexual transmission of ZIKV from infected men.[46] Should vaccine supply not be limiting, or should severe outcomes of ZIKV infection or transmissibility unique to males be identified, vaccination could be expanded to males. Reproductive age span defined as 15-49 years of age.[47] Depending on the country situation, lower bound could be reduced to 9 years of age if this would ease programmatic and cost-effective delivery of

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			the vaccine, based on experience of delivering HPV vaccine. Exclusions may need to be formulated in relation to subjects that are at increased risk of developing GBS and related illnesses. Vaccination should be indicated regardless of prior flavivirus exposure and vaccination history.
Vaccine platform	Non-replicating platforms with no documented safety concerns from use during pregnancy, such as inactivated whole, subunit based and those that use alum as adjuvant. Platforms which have licensed human vaccines within their class. Inactivated /virus-like particle, subunit vaccines are preferred from the safety perspective given the exposure of pregnant	Single-cycle replicating vector platform with robust safety data. A live, attenuated or replication competent viral vaccine platform (e.g. chimeric) with acceptable safety data, such as from inadvertent use during pregnancy. Alternative adjuvants to alum with extensive safety data, including from use during pregnancy.	The development of replication-competent vaccine platforms is not discouraged. However, there is a theoretical risk that live attenuated or replication-competent viral vaccines given to pregnant women may be capable of crossing the placenta and infecting the foetus, and for this reason, live vaccines are not recommended for use during pregnancy. That said, live-attenuated vaccines have been given to women of reproductive age (MMR, YF, polio) in situations of increased risk of exposure, and inadvertent vaccination of pregnant women does occur in mass vaccination campaigns, and to date there is no evidence of increased adverse pregnancy outcomes due to immunization with a live-attenuated vaccine[48]. However, the grade of attenuation and absence of neurotropic properties for a live ZIKV vaccine would have to be well-characterized before use due to the pathogenic characteristics of the wild type virus. As such, the safety assessment and regulatory requirements are likely to require additional data compared to a non-replicating vaccine platform (see safety). Non-replicating vaccine platforms that either do not use any adjuvant or use a well-characterized adjuvant in currently licensed vaccines, such as aluminium salts (e.g., Alum), would be preferable.

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	Preferred	**Minimal**	
	women.		The use of other adjuvants may, however, be justifiable, if accompanied with superior performance and delivery aspects (e.g. reduced number of doses). For sub-unit based vaccines, in particular, evidence of protective immune responses needs to be well-documented. Live vaccines should be accompanied by additional safety data related to assessment of neurovirulence, risk of reversion, risk of shedding and mosquito transmission. Vaccines based on replication-competent platforms are likely to have profiles more suitable for Scenario B (routine/endemic transmission) use.
Safety/ Reactogenicity	Safety and reactogenicity at least comparable to WHO-recommended routine vaccines, providing a highly favourable risk-benefit profile, ideally with only mild, transient adverse events related to vaccination and no serious AEs related to vaccination. Low risk of high fever.	Tolerable reactogenicity and acceptable safety profile where vaccine benefits outweigh safety risks; platform technologies should have extensive safety data from relevant applications, and at least observational data on the inadvertent or other use during pregnancy are desirable.	It is anticipated the clinical development programme should include demonstration of acceptable safety in representative age groups, both women and men, and in flavivirus-naive and -exposed subjects in the target population. Vaccine technologies that are considered safe in the target population group, and that are not contra-indicated in pregnant women for other vaccines should be favoured. It is highly desirable that at least observational data on the use of the platform technologies in pregnant women are available and have not shown a safety concern. For some products, observational data on the safety of live-attenuated vaccines when used in pregnancy are available, and no safety signal has so far been detected.[48]

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			In addition, data on inadvertent vaccination during pregnancy should be collected systematically, including safety data ante-partum, post-partum, and infant follow-up. Such information will be important for recommending bodies to advise on the use of the product in pregnant women. Absence of data supporting safe use of the vaccine in pregnant women must also be stated. Pregnancy registries or equivalent reporting mechanisms should be put in place before roll-out of the vaccine. Adverse event of special interest (AESI) should include: • Guillian-Barré Syndrome (GBS): Should studies of ZIKV-related GBS implicate a specific antigen in molecular mimicry, study of that antigen and immune responses against it need to be conducted. Should a direct pathogenic effect of the virus be confirmed, specific safety studies will be needed for live-attenuated vaccines. For all vaccine platforms, the risk of GBS will need to be monitored post-authorization. • Autoimmune disorders • Fever ≥ 38^{o}C • Severe disease with prior or subsequent flavivirus infection (in particular dengue) For all vaccine platforms, it is assumed that reproductive toxicology in a relevant model (lack of teratogenicity) will need to be conducted.
Measures of Efficacy	Demonstration of prevention of virologically confirmed	If a surrogate of immunity is established through animal models or cohort	The vaccine should preferentially have demonstrated efficacy against a well-defined clinical endpoint (e.g., prevention of ZIKV-associated disease of any severity compared to control, or prevention of

Vaccine characteristic	TPP for Emergency use		Product development considerations and assumptions
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	ZIKV illness, in accordance with proposed PAHO definition[45] in 80% of the population or higher. Evidence of prevention of infection.	studies, a reasonable assumption is a ZIKV-specific neutralising antibody titre, to be specified, in >70% of vaccinated population.	viraemia). If such trials are infeasible, and if an acceptable analytically validated immunologic correlate or surrogate of protection is identified, safety and immunogenicity studies may be considered, along with other supportive data (see below). If a surrogate is used, the efficacy threshold may need to be stratified by known prior exposure to other flaviviruses (in particular dengue). If immunological endpoints are used as the basis of authorization, vaccine effectiveness needs to be demonstrated as a follow-up commitment. In the absence of established parameters of risk, and with the evolving epidemiology with respect to the incidence of ZIKV infection and subsequent pathologies, the public health priority will be on reduction of clinical ZIKV disease in the vaccinated subject. Prevention of infection, either through prevention of viraemia (potentially measured regularly collected saliva or urine specimens) or prevention of seroconversion, may be an alternative to clinical illness. Reduction in viraemia levels could be a useful exploratory endpoint. The reduction in congenital abnormalities and the effect on GBS as exploratory outcomes, which, due to their low incidence, may only be assessed as a follow-up commitment. At a minimum, pre-vaccination serum samples should be collected from all participants in all trials to allow for analysis of safety, immunogenicity, and efficacy by flavivirus exposure at the time of vaccination, although testing may be driven by scientific need.

Vaccine characteristic	TPP for Emergency use		Product development considerations and assumptions
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			Pending study approval by regulatory authorities, data from a human challenge model may complement immunogenicity data. A vaccine with impact against transmission is highly desirable although would not be seen as a prerequisite in the emergency use scenario.
Dose regimen	Single dose primary series.	More than one dose. If multiple doses are required, a short interval between doses is preferred given the need to mount immunity rapidly in the context of an outbreak.	It is possible that pre-existing immunity to other flaviviruses such as dengue may prime the immune response to a ZIKV vaccine. It would be useful to measure the neutralising antibody titres to ZIKV and other flaviviruses, pre- and post-vaccination to evaluate, in individuals previously infected with or immunized against a flavivirus(es), the need for more than one dose in the primary series and also the need and spacing of booster doses.
Durability of protection	Confers long-lasting protection of more than 1 year after administering the primary series and can be maintained by a single booster dose	Confers protection of at least 1 year after primary series and can be maintained by booster doses If a booster is required, it should be no more than once annually, or at the time of a new outbreak.	Data on the duration of protection may be limited in the context of vaccine development for outbreak/emergency use; therefore, estimates of duration of protection will likely be based on kinetics of immune responses. At a minimum, the response kinetics should be suggestive of a clinical benefit for the duration of the outbreak and must cover the gestational period and the Zika transmission season. In addition, evidence should be available that indicate that the immune response can be maintained, if not boosted, by repeat vaccination. The role of immunity to other flaviviruses and the potential benefit of cross-protection should be evaluated and considered. Modelling of the immune responses, including assessment of T-cell memory over longitudinal studies, is highly

Vaccine characteristic	TPP for Emergency use		Product development considerations and assumptions
	Preferred	**Minimal**	
			desired.
Route of Administration	Injectable (IM or SC) using standard volumes for injection.		Standard routes of vaccination are preferred, but oral or sub-lingual delivery would be considered. ID administration could be considered if it constitutes a dose-sparing option and causes no undue safety concern.
Species coverage	Monovalent against ZIKV with documentation of neutralization of both ZIKV lineages (Asian and African).		
Product Stability and Storage	Shelf life of at least 12 months at -20°C. and Shelf life of at least 6 months at 2-8°C or above. The need for a preservative is determined and any issues are addressed.* VVM: Proof of feasibility and intent to apply a vaccine vial monitor (VVM) to the primary container.	Shelf life of at least 12 months at -20°C. Demonstrated stability for at least 6 hours at 2-8°C.[18] The need for a preservative is determined and any issues are addressed.	Storage at -20°C assumes this is not an alum-adjuvanted vaccine. *WHO-approved preservatives for multi-dose vials include thiomersal and 2-phenoxyethanol (used for inactivated polio vaccine).[49,50]
Co-administration with other vaccines	The vaccine can be co-administered with other vaccines	The vaccine will be given as a stand-alone product not co-administered with	Stand-alone administration during an emergency or outbreak situation would be acceptable for deployment; however data on co-administration data with other vaccines, particularly other flavivirus

Vaccine characteristic	TPP for Emergency use		Product development considerations and assumptions
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	licensed for the same age and population groups without clinically significant impact on immunogenicity or safety of the Zika vaccine or the co-administered vaccines.	other vaccines.	vaccines, would be favourable. Co-administration with HPV, tetanus, inactivated influenza, Tdap, Dengue and YF vaccines, etc. depending on recommended in-country immunization schedule indicated for target population.
Presentation	Vaccine is provided as a liquid product in mono-dose or multi-dose (5-10) presentations with a maximal dosage volume of 0.5mL for i.m. or s.c. administration. Multi-dose presentations should be formulated, managed, and discarded in compliance with WHO's multi-dose vial policy[24]	Vaccine is provided as a lyophilized product in mono-dose or multi-dose (5-10) presentations with a maximal dosage volume of 0.5mL for i.m. administration. Multi-dose presentations should be formulated, managed, and discarded in compliance with WHO's multi-dose vial policy Lyophilized vaccine will need to be accompanied by paired separate vials or ampoules of the appropriate diluent	In line with Vaccine Presentation and Packaging Advisory Group (VPPAG) generic preferred product profile (gPPP).[51] Preferred and minimal dose volumes may vary depending on route of administration. See note in 'Product Stability' on preservatives.

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