

1 Targets, Medical Need, Product Objective, Scope, Description of Technology, Use Cases, and Integration:

WHO and TPP Targets: The Target Product Profile (TPP) responds to the WHO target of reducing the dengue burden globally by 25% by 2030 (WHO, 2020) and a preferred target of reducing the dengue burden nationally by 25% by 2030. The TPP defines the performance and cost characteristics of <i>Wolbachia</i> replacement product(s) that would be required to enable countries to achieve this global WHO or national target. The TPP targets are meant to guide product developers, national regulators, and their potential funders to assess candidate products to determine whether they meet, or have the potential to meet, the requirements. The TPP does not represent WHO guidance to countries for implementation of <i>Wolbachia</i> replacement technologies which will be addressed separately. The ‘Context and Background Materials’ annexed to this TPP explain the derivation and definition of the cost targets.
Medical Need: The <i>Aedes aegypti</i> mosquito is the principal vector of dengue, chikungunya, Zika and yellow fever viruses. Dengue incidence has been rising and the WHO Global Vector Control Response 2017 – 2030 reports an estimated 96 million symptomatic cases, 1.9 million DALYs and over 9,110 deaths per year. The only vaccines are for yellow fever and for dengue seropositive individuals aged 9–45 years old, though there are other dengue vaccine candidates in clinical trials (Izmirly <i>et al.</i> 2020). There are no drugs available to combat these infections and disease prevention largely relies on community-based vector control. Effective control of this vector is difficult to achieve and sustain, given the mosquito’s high reproductive rate and adaptation to urban habitats. The mosquito eggs can survive desiccation and the larvae develop in artificial containers, including cryptic or hard to find habitats in the urban environments. The impact of current measures such as source reduction and chemical treatment is difficult to sustain and short-lived.
Product Definition and Objective: The product is <i>Ae. aegypti</i> carrying a strain or strains of <i>Wolbachia</i> that reduce the ability of the mosquito to transmit arboviruses, in a suitable format for release in campaigns to replace the local <i>Ae. aegypti</i> population. The objective of the product is to be affordable for local purchase, deployable in a way that is safe, registrable, acceptable to the local health authorities and local population, capable of achieving an average of not less than 70% reduction in dengue incidence in endemic areas where deployed, and to be deployable in sufficient areas to enable achievement of the WHO target of reducing by 25% the global dengue burden by 2030 (from 2010 -2020 baseline) (WHO, 2020). The 70% dengue reduction achieved on average, in endemic areas (where the disease is present every year though may vary between years) where deployed, should be sustained for at least 3 years, preferably 10 years or more. As a preferred target it should be deployable in sufficient settings to enable a reduction by 25% of national dengue burdens by 2030 in at least 95% of countries in dengue endemic regions, as well as providing control of other <i>Ae. aegypti</i>-borne viruses. (This TPP focuses on dengue given it is the <i>Ae. aegypti</i>-borne disease with the highest incidence and for which WHO goals are published).
Scope: This TPP describes the requirements of the product and its production, for it to be deployable in campaigns involving releasing these mosquitoes to replace the local <i>Ae. aegypti</i>, to enable achievement of the WHO global goals for dengue reduction (WHO, 2020). Production requirements and cost targets (including product costs and total costs of achieving target coverage levels), to ensure affordability in sufficient areas to reach the global goals, are also described. Although the TPP’s ‘Total cost of coverage’ targets include all such costs, the TPP does not specify the range or variety of operational activities related to the establishment of required levels of <i>Wolbachia</i> coverage in specific settings.
Description of Technology: Releases of a strain of <i>Ae. aegypti</i> carrying the endosymbiotic bacterium <i>Wolbachia</i> that mates with local (uninfected) <i>Ae. aegypti</i> and causes an increasing proportion of the local mosquito population to have <i>Wolbachia</i>. This process is driven by two factors: 1) <i>Wolbachia</i> being maternally dominant (female passes on <i>Wolbachia</i> to her progeny) and 2) induction of cytoplasmic incompatibility (where <i>Wolbachia</i> infected males suppress the production of offspring when they mate with uninfected, local females). Once a sufficiently high proportion of the targeted <i>Ae. aegypti</i> population harbours <i>Wolbachia</i>, the releases can be stopped or scaled back, and the <i>Wolbachia</i> is maintained in the population. The strain of <i>Wolbachia</i> used renders its mosquito host refractory to dengue virus, and therefore as the <i>Wolbachia</i> frequency increases in the mosquito population, that population becomes less capable of transmitting this virus.
Use Cases and Integration with Other Control Activities: The two principal use cases are: (1) Turnkey - the producer provides a complete solution to the local governmental, state or national customer, or private sector customer; (2) Integrated - the supplier provides <i>Ae. aegypti</i> infected with <i>Wolbachia</i> and the local public/governmental user, or third party undertakes community engagement, release, monitoring and integration with other vector control activities. Integration with methods that suppress the <i>Ae. aegypti</i> population is not covered in this TPP.

2 TPP requirements (defined in the Use Case Characterization)

Category and Requirement	Minimum <i>The minimal target should be considered as a potential go/no go decision point.</i>	Preferred <i>The preferred target should reflect what is needed to achieve broader, deeper, quicker global health impact.</i>	Annotations <i>For all parameters, include here the rationale for why this feature is important and/or for the target value.</i>
Product Performance			
Reduction in human viral infections	In deployments of the first product in this class (type) in dengue endemic areas in which <i>Ae. aegypti</i> is the vector, laboratory confirmed dengue case incidence is reduced compared to baseline and comparable areas without <i>Wolbachia</i> by an average of not less than 70% (based on a minimum of 2 trials of sufficient scale, meeting VCAG standards, with epidemiological endpoints, submitted to WHO for assessment). The product is deployable cost-effectively in sufficient areas to enable the WHO target of reducing by 25% the global dengue burden by 2030 (from 2010 -2020 baseline) [This represents the total area potentially accessible to the product at the costs indicated in the 'Total cost of coverage'].	In the areas in which <i>Ae. aegypti</i> is the vector and the product is deployed, confirmed dengue case incidence is reduced compared to baseline or comparable areas without <i>Wolbachia</i> by an average of not less than 70% (tested in a minimum of 2 epidemiological trials in different endemic settings of sufficient scale, meeting VCAG standards, and with additional modelling to predict performance elsewhere). The product is deployable cost-effectively in sufficient areas to enable a reduction of 25% national dengue burden by 2030 (from 2010 – 2020 baseline) for at least 95% of dengue endemic countries [This represents the total area potentially accessible to the product at the cost indicated in the 'Total cost of coverage'].	The targets for the WHO Global Strategy for Dengue Prevention and Control 2021 – 2030 are described in https://www.who.int/publications/i/item/9789240010352. The Utarini <i>et al.</i> (2021) trial in Yogyakarta demonstrated 77% reduction in dengue incidence (https://www.nejm.org/doi/full/10.1056/nejmoa2030243). Modelling by O Brady (Context & Background Materials) indicates that this level of reduction in dengue incidence is expected to be achieved on average for equivalent implementations of this product in dengue endemic urban settings, but it will be advisable to generate further empirical evidence to verify this in selected settings. The Minimum level of efficacy exceeds the general standard required by VCAG but represents an achieved level which follow-on products should also achieve. Dengue incidence may also be reduced in epidemic regions, but the WHO global dengue reduction goal could be achieved by deploying only in endemic countries, and therefore being deployable there is the focus of this TPP. Individual countries need to assess whether the

			evidence for the product is sufficient for implementation in their own circumstances and epidemiological setting. Additional trials may be required. Where a significant proportion of transmission is by <i>Ae. albopictus</i>, the 70% reduction in dengue incidence may not be achieved. The approach is preventative and therefore not suitable for tackling an existing dengue outbreak. Effectiveness for chikungunya, Zika and yellow fever, are also desirable but not included in the targets given difficulty in conducting trials.
Target coverage (proportion of <i>Aedes aegypti</i> with <i>Wolbachia</i> in the areas where the product is released)	After repeated releases of <i>Ae. aegypti</i> with <i>Wolbachia</i> > 90% of the local <i>Aedes aegypti</i> population have <i>Wolbachia</i> . On a sustained basis this does not drop below 80%.	Same as Minimum.	These targets are achievable with current <i>Wolbachia</i> technology. High coverage is generally required in order to provide a high level of reduction in the mosquito population's capability to transmit disease, though there are examples and modelling showing that significant reductions in dengue can occur at even 50% coverage (and therefore there is a benefit before coverage rises to 90%).
Time to achieve target coverage in a specified area, after releases initiated	Scenario 1: On average, target coverage is achieved no more than 1 year after starting releases in each area (municipality) where the product is deployed. Scenario 2: Across the <i>Wolbachia</i> campaign area, an average of at least 50% coverage is achieved within 1 year and target coverage is achieved within 3 years.	On average, target coverage is achieved no more than 6 months after starting releases in each area (municipality) where the product is deployed.	Experience with releases and modelling of releases demonstrate that 6 – 12 months is achievable, though the duration could be influenced by egg banks. Timing in relation to the rainy season will affect time to achieve target coverage. A longer release period of low intensity releases that stops at around 50% coverage might reduce cost by minimizing the number of releases, and increasing acceptance from the local population, but would extend the time before benefits occurred. Deployments with deliberate geographical gaps that will be filled in naturally would also reduce cost but extend time.

Duration of coverage following the achievement of target coverage	Target coverage (corresponding to target disease incidence reduction) sustained for at least 3 years after it has been achieved. Provided coverage remains above target, disease incidence reduction effect is maintained.	Target coverage (corresponding to target disease incidence reduction) sustained for at least 10 years after it has been achieved. Provided coverage remains above target, disease reduction effect is maintained.	The duration of the reduction in disease incidence is key to its usefulness. <i>Wolbachia</i> wMel is capable of being sustained in the <i>Aedes aegypti</i> population, resulting, in most endemic situations, in a long-term reduction in the transmission of virus. There is an expectation after achieving 3 years of target coverage that at least 5 years will be achieved. This needs to be verified after 5 years.
Release procedures	The number and duration of releases, the number of release events, the method and pattern of releases, and the number of mosquitoes released each time, in order to achieve target coverage, must be within the required cost and regulatory requirements and acceptable to residents and the vector control programme.	Same as Minimum	Modelling shows that rounds of releases every two weeks at a ratio of 0.1x or 0.05x the local <i>Ae. aegypti</i> population should be sufficient to achieve 95% coverage with <i>Wolbachia</i> within 6 – 12 months after releases commence. Experience has shown that for implementation a release ratio of 0.2x can be used and the <i>Ae. aegypti</i> population then monitored to check the initial coverage in order to calibrate future releases. In trials, the release ratio can be assessed for adult <i>Ae. aegypti</i>, using mark-release-recapture, but this is costly for deployment. High frequency, long duration and high relative numbers released are costly and less acceptable to residents than low frequency and short duration and low relative numbers released. Protected eggs are currently lowest cost option and allow releases to be continuous, giving more impact and avoiding pulses of increased biting rates. Releases need to continue until the threshold coverage for establishment is achieved. This threshold value is an operational matter and does not need to be set as a TPP requirement in addition to the number of releases and the number released.

Releases following achievement of target coverage	If needed to maintain the <i>Wolbachia</i> coverage above target, the requirement for gap-filling releases (or releases at the edge of the treated area), after achievement of target coverage, should not exceed 1 release every 2 years and 25% of the release area.	There is no ongoing requirement for releases to maintain the proportion of the population with <i>Wolbachia</i> above threshold in dengue endemic countries.	While most circumstances with wMel or other strains should not require top-up releases, some strains may require top-up releases dependent on local factors which are difficult to measure, e.g., size of egg bank and local ecology, as well as fitness of mosquitoes released. There is some evidence of an association between elevated temperature and seasonal variation in <i>Wolbachia</i> coverage in a small trial in Vietnam (https://gatesopenresearch.org/articles/5-147). This may lead to the need for a temperature resistant strain of <i>Wolbachia</i> in certain situations and/or top-up releases.
Vector fitness and Cytoplasmic Incompatibility (CI)	Before proceeding to field trials with a new <i>Ae. aegypti</i> <i>Wolbachia</i> replacement product, laboratory tests should be conducted on the <i>Ae. aegypti</i> with the relevant strain(s) of <i>Wolbachia</i>, to check: • fitness is not so low compared to wild type mosquitoes as to jeopardize the likelihood for establishment of the <i>Wolbachia</i> infection within the specified coverage parameters, and CI is maintained (measured for example by Fried test, fecundity and CI) • the <i>Wolbachia</i> is inherited reliably (maternal transmission test) • the <i>Ae. aegypti</i> to be released does not have a significantly different insecticide resistance profile to the average for the local population in the release sites. (If a difference is found it will be necessary to backcross to the native mosquitoes and re-verify). Also see 'Background genetic material'.	Same as Minimum	Fitness measured in the lab is not a reliable indicator of fitness in the field but should be checked for new strains of <i>Wolbachia</i> to ensure no major fitness penalty. Insecticide resistance in the field may be patchy and therefore sufficient sampling of the native population needs to be carried out to check that the introduced mosquitoes are a representative match in terms of resistance profile.

TPP *Wolbachia Aedes aegypti* replacement – Final Version February 2022

Vector competence	There is a sufficient reduction in vector competence for the dengue virus serotypes that are present in the intended location of trials or deployment (in the <i>Ae. aegypti</i> with the <i>Wolbachia</i> strain(s) compared to the wild type, to predict an effective reduction in transmission in field deployment. Standard methods should be used for this (based on % of mosquitoes with virus detected in their saliva at least 7 and 14 days of after ingestion) and results referenced against other strains of <i>Wolbachia</i> with known transmission reduction in field deployment.	Same as Minimum	
Product characteristics			
Total cost of coverage (including product and deployment) for the area in which the product is released	Scenario (1) (see 'Time to achieve target coverage') Total <i>Wolbachia</i> cost of coverage (including product cost) per person to meet the Minimum target for 25% reduction of dengue burden globally $\leq$ US\$2.33 to equal 5 years of averted medical costs plus averted outbreak control programme costs. Scenario (2) (see 'Time to achieve target coverage') Total <i>Wolbachia</i> cost of coverage (including product cost) per person to meet the Minimum target for 25% reduction of dengue burden globally $\leq$ US\$1.44 to equal 3 years of averted medical costs plus averted outbreak control programme costs.	Total <i>Wolbachia</i> cost of coverage (including product cost) per person to meet the Preferred target for 25% reduction of dengue burden nationally $\leq$ US\$0.24 to equal 3 years of averted medical costs plus averted outbreak control programme costs.	Costs based on modelling by O Brady. For details of assumptions and calculations see Context & Background Materials which are incorporated by reference into and with this TPP. The target costs are those that needs to be met to achieve fully the stated goals and, therefore, the costs in the areas that need to be treated that have the lowest avertable medical and outbreak control programme costs. The replacement technology cost profile is front-loaded, with benefits extending for several years: this does not match the pattern for most other vector control interventions. Countries might see additional important advantages beyond averting medical costs, such as reduction in morbidity and mortality.

TPP *Wolbachia Aedes aegypti* replacement – Final Version February 2022

			Willingness to Pay analysis is anticipated to support the stated target costs. Variability in acceptable cost will occur due to differences in cost of implementation in different environments and Willingness to Pay in specific markets.
Cost of final product (in deployable format, imported or ex production facility in the country in which it is deployed, including all costs related to manufacture and storage, but excluding manufacturer's margin, release costs and other deployment costs)	Scenario (1) (see 'Time to achieve target coverage') Average product cost per person to meet the Minimum target for 25% reduction of dengue burden globally $\leq$ US\$0.43 to correspond to 5 years of averted medical costs plus averted outbreak control programme costs). Scenario (2) (see 'Time to achieve target coverage') Average product cost per person to meet the Minimum target for 25% reduction of dengue incidence globally $\leq$ US\$0.27 to correspond to 3 years of averted medical costs plus averted outbreak control programme costs.	Average product cost per person to meet the Preferred target for 25% reduction of dengue incidence nationally $\leq$ US\$0.044 to correspond to 3 years of averted medical costs plus averted outbreak control programme costs.	As further described in the Context & Background Materials which are incorporated by reference into and with this TPP, these targets are derived from the Total cost of coverage targets (above) based on release site budget items from previous release programmes, indicating that on average 18.6% (range 10.1 - 44.3%) of costs are directly related to production. (Includes start-up costs, rearing, rearing diagnostics and a proportion of overheads, administration and management.) Initial production would be expected to be more costly and subsequent volumes would reduce in cost. The product cost targets assume no leveraging of existing vector control programme costs (i.e., turnkey implementation model).

TPP *Wolbachia Aedes aegypti* replacement – Final Version February 2022

Regulatory standards	Meets relevant standards of national regulatory authorities for registration, or in the absence of relevant established national regulatory schemes, demonstrates registrability through achievement of regulatory approval for field testing, in at least 2 of the WHO top 20 priority countries for dengue. A regulatory pathway to full implementation, with no known barriers that would prevent the product's registration, needs to be identified. Meets applicable standards for transport and importation.	In the absence of established national regulatory schemes for this product in dengue endemic countries, registrability needs to be demonstrated through achievement of approval for field testing in at least the WHO top 20 priority countries for dengue, and a regulatory pathway needs to be agreed to full implementation, with no known barriers that would prevent the product's registration. Meets applicable standards for transport and importation.	The WHO maintains an updated list of the priority countries for dengue, based on reported cases over the last 10 years. In January 2022 it is Brazil, Philippines, Pakistan, Mexico, Vietnam, Indonesia, Thailand, India, Colombia, Malaysia, Sri Lanka, Nicaragua, Paraguay, Honduras, Yemen, Peru, Venezuela, El Salvador, Cambodia and Bolivia. Where regulatory schemes do not exist for this product, this requires engagement with the country regulators to agree suitable standards. Ideally also registrable by a major regulatory authority (i.e., EPA, EU, Australia, Canada).
WHO standards	Meets relevant WHO standards.	The product is able to demonstrate public health value to VCAG standard or is accepted by WHO to fit the existing WHO product class. It meets requirements for listing by PQ (verification may require dialogue with PQ).	It will be helpful for the product to be covered by WHO operational guidelines along with PQ listing.
Human Risk / Benefit Assessment	An acceptable risk assessment of the <i>Wolbachia</i> strain to demonstrate no increased incidence of representative human arboviral infections, including Zika and Chikungunya, due to <i>Wolbachia</i> infected <i>Aedes aegypti</i>-borne pathogens (measured by vector competence and biting rate).	Same as Minimum.	
Background genetic material	Will not result in deleterious phenotypic changes in the local <i>Ae. aegypti</i> population, such as increased insecticide resistance (measured by WHO test methods and checking that the introduced <i>Ae. aegypti</i> do not contain known resistance genes that are absent in the local <i>Ae. aegypti</i> population).	Same as Minimum.	Back-crossing on a highly localized basis is uneconomic and so it needs to occur nationally or regionally provided no deleterious genes introduced and regulatory requirements are met.

TPP *Wolbachia Aedes aegypti* replacement – Final Version February 2022

Other environmental impact	No negative effects on <i>Ae. aegypti</i> predator or prey species.	Same as Minimum.	
Community acceptability	The increase in nuisance biting rate through the 'Release characteristics' is acceptable to the local residents.	Residents do not perceive any increase in the nuisance biting rate due to the releases.	A Public Acceptance Model (if available) may be used to manage public acceptance. The nuisance effect of any increase in biting may not be perceived where nuisance biting is dominated by <i>Culex</i> . The whole campaign needs to be acceptable to residents (including through community engagement activities if necessary), but this is a local, operational issue and not a product attribute.
Production and delivery			
Accessibility (availability) for procurement	Suitable (including registrable) for indigenous production or import and purchase by national and municipal authorities in dengue endemic countries.	Suitable (including registrable) for indigenous production or import and purchase by national and municipal authorities in dengue endemic and epidemic countries.	
Production quantity	Product can be manufactured in sufficient quantities to enable achievement of the minimum performance and cost targets.	Product can be manufactured in sufficient quantities to enable achievement of the preferred performance and cost targets.	PQ assessment could be requested.
Quality Assurance (of manufacturing process and product production)	Product not intrinsically susceptible to quality variation in production in terms of the parameters which affect performance and other product requirements. For each strain to be released, batch consistency is demonstrated by laboratory assessment of fitness and CI characteristics (Fried test, fecundity, CI, maternal transmission, hatch rates, sex ratio etc.).The proportion of mosquitoes that are released which do not have <i>Wolbachia</i> must meet regulatory standards and be less than 2%.	Same as Minimum, but all mosquitoes that are released must have <i>Wolbachia</i> .	This is part of the PQ listing process.

TPP *Wolbachia Aedes aegypti* replacement – Final Version February 2022

Product packaging, transport, storage and distribution)	Suitable for distribution and release and deployable in a reproducible, standard way in a wide variety of settings.	Same as Minimum.	
Channel to market opportunities and partnerships	Commercial (or government) interest demonstrated by potential partners with the necessary implementation capability, e.g., sales, production scale-up, manufacturing, distribution, logistic, surveillance, community engagement and regulatory capabilities in the affected countries, and with the interest to register the product and implement campaigns with it in line with the areas to be treated to meet the Minimum Product Performance requirements.	Same as Minimum	Adequate margin is required above product cost to enable commercialization
Intellectual Property			
IP (Protection of Intellectual Property)	Freedom to Operate: product and production methods do not contravene 3 rd party IP. Potential exists for new IP, suitable for license to manufacturing partner.	Same as Minimum	

3 References

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