Context and Background Materials

In Support of the WHO Technical and Scientific Advisory Group with Respect to the Development of:

- a Target Product Profile (TPP) for a Wolbachia Spp. Strain (Aedes Aegypti Population Replacement Product), and
- a Preferred Product Characteristics (PPC) Document for Potential Combinations of Wolbachia Aedes aegypti population replacement approach and other Aedes aegypti population suppression products

Executive Summary

With the successful demonstration of Wolbachia Aedes aegypti population replacement method and its impact on dengue,¹ the groundwork has been laid for a global effort to use Wolbachia to control/eliminate dengue. To date, however, both Wolbachia replacement and suppression method approaches have largely been deployed at pilot or demonstration scale and largely in very particular kinds of areas (dense high burden cities). The challenge now is replicating these results at a scale sufficient to substantially reduce the global burden of dengue. The WHO goal to reduce global incidence by 25% by 2030 provides a framework for setting expectations on how generalizable replacement programs need to be. Based on these WHO targets, a modelling framework has been developed that suggests a range of effectiveness and cost targets for Wolbachia replacement approaches. This modelling, as described in detail herein, can support the TAG as it seeks to set quantifiable TPP targets. In addition, and as described herein, a range of implementation models are possible and should be discussed, including a “hybrid” program of suppression followed by replacement. These various implementation models may have an impact on the cost efficacy and generalizability of Wolbachia replacement approaches. Therefore, the generation by the TAG of a PPC for such hybrid approaches is appropriate.

Background. The Aedes aegypti mosquito is the principal vector of dengue, Zika, yellow fever and chikungunya viruses. Dengue incidence has been rising and the WHO Global Vector Control Response 2017 – 2030 reports an annual 96 million cases, 1.9 million DALYs and 9,110 deaths. Vaccines are only available for yellow fever and for dengue seropositive individuals 9–45 years old in dengue endemic countries, though there are other dengue vaccine candidates in clinical trials.² There are no drugs available to combat these infections and so there is a reliance on prevention through 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, with an egg stage that can survive desiccation and a larval phase that can develop in small, temporary water volumes (e.g., water containers and roof gutters). The rapid growth of cities has also favoured this mosquito. As a result, existing vector control tools alone have

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generally been unable to sustainably control it or the diseases it transmits over the long term, and a range of novel technologies are under development. These include biocontrol through use of *Wolbachia* spp. for population replacement or reduction/suppression, the release of mosquitoes carrying a dominant lethal gene (“RIDL”), and other forms of sterile insect technique (“SIT”).

*Wolbachia* spp. for population replacement method or reduction/suppression method has been described as follows:

Mosquitoes with *Wolbachia* (i) are less likely to internally disseminate dengue, chikungunya, Zika, and yellow fever viruses and thus are less likely to become infectious, and (ii) can suppress or replace the natural mosquito population due to fatal cytoplasmic incompatibility which means that *Wolbachia*-infected males suppress the production of offspring when they mate with uninfected, local females. *Wolbachia* can, therefore, be used to either replace the existing mosquito population with a lower competence phenotype or suppress the existing population by releasing only males. Replacement programs with *Wolbachia* entail substantial initial investments to establish *Wolbachia* in the mosquito population through intensive releases at the beginning of the program but potentially offer considerable long-term benefits. The replacement approach contrasts with suppression strategies with *Wolbachia*, sterile insect techniques, or conventional vector control tools, which need ongoing application.

It should be noted that the cost dynamics of replacement and suppression with current insecticides and larvicides are very different. Replacement may involve higher upfront costs but then a long duration of effectiveness -- previous replacement programs have seen durability of self-sustaining high *Wolbachia* coverage for over a decade despite ongoing use of insecticides and major weather events at relatively minimal ongoing cost. Suppression (with conventional tools such as insecticides) have low set up costs if compatible with existing vector control programme activities but, unlike with replacement, require ongoing costs. Conventional insecticides also have a relatively short duration of effect (relative to replacement), with benefits realized shortly after the costs. Thus, the cost dynamics of the replacement method are closer to those of vaccines than conventional vector control products. Novel suppression methods such as release of male only *Wolbachia*, RIDL or SIT, will require new initial investment in rearing capacity and in machinery/technology for sex sorting or irradiation, but could potentially offer either lower costs or higher effectiveness than conventional vector control products over the longer term.

All of these individual novel technologies (*Wolbachia* replacement, *Wolbachia* suppression, RIDL, or SIT) have been and continue to be the subject of ongoing development, evaluation, demonstration and scale-up in various high burden programmatic and private settings. In addition, as an alternative to any of these individual novel technologies or methods, there is the potential to combine *Wolbachia* population

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3. Note: These novel technologies share several scale-related challenges. First, these novel technologies are dependent upon broad community acceptance, and thus require significant community engagement and advocacy, at least at the initial stages of deployment. Second, these novel technologies require sophisticated and ongoing mosquito surveillance to confirm the establishment and or effectiveness of the technology intervention. However, there are opportunities to mitigate these challenges by closer integration with existing vector control and related community engagement and monitoring programs and resources.


replacement technology with other suppression technologies in ways that might be synergistic from a cost, community acceptance (reduced exacerbation/nuisance), or dengue incidence reduction perspective. Specifically, a program of suppression followed by replacement could increase the chances of successful Wolbachia establishment and reduce the cost of, and exacerbation/nuisance associated with, achieving such establishment, provided suppression does not adversely affect spatial dispersal of released Wolbachia mosquitoes.

As work continues to develop, evaluate, and scale these novel technologies and approaches, the WHO's recent Call for Experts clearly focuses more narrowly on the Wolbachia Aedes aegypti population replacement product/approach and on potential hybrid approaches involving Wolbachia Aedes aegypti population replacement product/approach. The Call for Experts defines the areas of focus for, and the role of, the Technical Advisory Group (“TAG”) as follows:

In its capacity as an advisory body to WHO, the TAG shall have the following functions:

1. To review and make recommendations on the development of a Use Case Description (or Descriptions) incorporating Case Objectives and Needs Statements, for (i) Wolbachia Aedes aegypti population replacement product/approach, and (ii) potential combination(s) of this approach with other Aedes aegypti control methods to be integrated into local Aedes aegypti control/management programmes.

2. To advise WHO and support the identification, development, of a TPP for a Wolbachia Aedes aegypti population replacement product. The targets and preferred characteristics are for a product and product combinations applicable globally and targeting the highest dengue burden countries in the world. This will include help with selection of the required characteristics and advice on proposed minimum and preferred standards for each of the characteristics.

Wolbachia Ae. aegypti Population Replacement Method. The Wolbachia Aedes aegypti population replacement method aims to replace the existing Aedes aegypti population with Ae. aegypti with Wolbachia. The approach involves regular releases of Wolbachia-infected mosquitoes into a wild mosquito population over a period of several months. Wolbachia facilitates its own increase in proportion (coverage) of mosquitoes within the population by manipulating reproductive outcomes between wild-type and Wolbachia-infected mosquitoes: the only viable mating outcomes between such pairs are those in which the progeny are infected with Wolbachia. Once a critical proportion of mosquitoes in the population have Wolbachia, Wolbachia coverage will continue to increase to fixation without further releases, but below this threshold Wolbachia coverage may decline (possibly to 0) once releases stop. Reaching this critical threshold is the key goal of Wolbachia replacement methods.

The efficacy of the Wolbachia Aedes aegypti population replacement method was evaluated in a cluster randomized controlled trial within Yogyakarta City, Indonesia. The aim of the study was to determine whether and to what extent Wolbachia replacement method was effective in reducing the incidence of symptomatic dengue and resulted in fewer hospitalizations. The results of this study, published in June

10 Call for experts: Technical Advisory Group (TAG) on the Development of a TPP for a Wolbachia spp. strain (Aedes aegypti population replacement product)
2021, confirmed a 77% reduction in dengue incidence and an 86% reduction in hospitalizations in areas in which Wolbachia was successfully established.\footnote{Utarini et al., Efficacy of Wolbachia-infected mosquito deployments for the control of dengue. N. Engl. J. Med. 384, 2177–2186 (2021).}

**Translation to Scale Challenges.** With the successful demonstration of Wolbachia Aedes aegypti population replacement method and its impact on dengue,\footnote{World Health Organization. “CLOSED SESSION.” Thirteenth Meeting of the WHO Vector Control Advisory Group, World Health Organization, 2021, pp. 1–18, \url{http://www.jstor.org/stable/resrep30089.4}; Utarini, A. et al. Efficacy of Wolbachia-infected mosquito deployments for the control of dengue. N. Engl. J. Med. 384, 2177–2186 (2021).} the groundwork has been laid for a global effort to use Wolbachia to control/eliminate dengue. To date, however, both Wolbachia replacement and suppression method approaches have largely been deployed at pilot or demonstration scale. Thirteen countries have implemented replacement programs at various levels of scale, with 12 through the World Mosquito Program (“WMP”) and an independent program in Malaysia. Meanwhile, China (with Ae. albopictus), Singapore, and the USA have so far chosen to use suppression-based programs due to perceived greater compatibility with their existing intensive and long-term efforts to suppress mosquito populations.\footnote{Brady, O.J., Kharisma, D.D., Wilastonegoro, N.N. et al. The cost of Vector Control: is this affordable, or acceptable as is required to support the emergence of demand for such novel technologies and approaches, the global community, under the auspices of the WHO, is convening the TAG to define the use case(s) and develop a target product profile (TPP). The quantified targets in the TPP will enable a gap analysis with respect to available technologies and help to drive further innovation including product, production, or use-pattern developments and to identify the circumstances where the technologies should be targeted.} There have been no large scale (national or regional), non-donor funded implementations of Wolbachia replacement or suppression approaches. The following excerpt from Scott Ritchie’s 2019 article entitled “Reflections from An Old Queenslander: Can Rear and Release Strategies Be the Next Great Era of Vector Control?” summarizes well some of the barriers to translation to scale:

> Even if community and regulatory approvals are provided, and pilot trials are successful, many hurdles to implementation at scale remain (\textit{table 2}). Research into technological fixes for mass rearing, releasing and even monitoring is under way. There are two huge expenses for rear and release programs, excluding communications: the production and release of massive numbers of mosquitoes, and monitoring.\footnote{Ritchie Scott A. and Staunton Kyran M. 2019 Reflections from an old Queenslander: can rear and release strategies be the next great era of vector control? \textit{Proc. R. Soc. B} 2862019097320190973 \url{http://doi.org/10.1098/rspb.2019.0973}.}

To assist Wolbachia replacement method innovators address the hurdles to implementation at scale listed in the table referenced above, to ensure that appropriateness, accessibility, affordability, and acceptability of these technologies, and thus to assist in the emergence of demand for such novel technologies and approaches, the global community, under the auspices of the WHO, is convening the TAG to define the use case(s) and develop a target product profile (TPP). The quantified targets in the TPP will enable a gap analysis with respect to available technologies and help to drive further innovation including product, production, or use-pattern developments and to identify the circumstances where the technologies should be targeted.

**Approach to the Establishment of TPP Quantified Targets.** As indicated, Wolbachia replacement method has not yet been deployed at large scale in non-donor funded programs. This indicates that, while highly effective, Wolbachia replacement method may not yet be (i) widely understood or recognized as a viable operational method, or (ii) available at sufficient scale or may not yet be as appropriate, accessible, affordable, or acceptable as is required to support the emergence of demand, and/or (iii) likely (or viewed as likely) to have a significant impact in reducing dengue incidence on a global or national basis. It is, therefore, imperative that the TPP establish quantified targets that are likely to drive further innovation to address these gaps and/or uncertainties and facilitate the emergence of funded demand.

\footnote{Call for experts: Technical Advisory Group (TAG) on the Development of a TPP for a Wolbachia spp. strain (Aedes aegypti population replacement product).}
To assist in this process, the following approach has been adopted:

1. **Identify the specific needs that align with a product being appropriate, affordable, accessible, and acceptable, and the corresponding product requirements that signal a need has been met.** These needs include:

   o **Safety:** Need to replace mosquito population in a manner that does not introduce significant risk of adverse events to targeted areas,
   o **Efficacy:** Need to replace mosquito population in a manner that achieves objectives for incidence, time to impact, and maintenance,
   o **Acceptability:** Need to replace mosquito population in a manner that is acceptable to the population in which it is introduced,
   o **Accessibility:** Need to replace mosquito population in a manner that is operationally accessible to all targeted populations through either indigenous production or import,
   o **Regulatory:** Need to replace mosquito population in a manner that can be effectively regulated in all targeted populations,
   o **Manufacturing:** Need to replace mosquito population in a manner that enables manufacturing best practices, including quality assurance, for biologics,
   o **IP:** Need to replace mosquito population in a manner that does not have any barriers with respect to FTO, and
   o **Cost:** Need to replace mosquito population in a manner that is affordable to all targeted populations.

   An overall product objective and a full list of measurable characteristics that relate to the above needs are given in the draft Target Product Profile (TPP) that accompanies this Context and Background document. Specific, quantifiable targets with respect to each of these characteristics also need to be defined in the Target Product Profile. A suggested approach to generating the quantifiable targets regarding efficacy and cost is detailed below.

2. **Identify efficacy needs based on WHO dengue reduction goals.**

   Efficacy of *Wolbachia* replacement programs is based on the successful establishment of *Wolbachia* at such levels and in such a manner as to deliver the level of effectiveness observed in the Yogyakarta RCT. The TPP will include and reflect quantified targets around such vector-related factors as coverage, fitness and other factors necessary to consistently deliver this level of effectiveness over a period of sustained transmission prevention.
Efficacy of *Wolbachia* replacement programs also is based on the ability of such an approach to have a significant impact toward achieving WHO dengue reduction goals. As stated by the WHO,\textsuperscript{17} dengue reduction goals for 2030 are:

<table>
<thead>
<tr>
<th>Indicator</th>
<th>2020 (baseline)</th>
<th>2023</th>
<th>2025</th>
<th>2030</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case-fatality rate due to dengue</td>
<td>0.80%</td>
<td>0.50%</td>
<td>0.50%</td>
<td>0%</td>
</tr>
<tr>
<td>Number of countries able to detect and respond to dengue outbreaks</td>
<td>10/128 (8%)</td>
<td>26/128 (20%)</td>
<td>64/128 (50%)</td>
<td>96/128 (75%)</td>
</tr>
<tr>
<td>To reduce the burden of the disease and its incidence by 25% (2010–2020 as baseline)</td>
<td>3 100 900</td>
<td>3 million</td>
<td>2.75 million</td>
<td>2.35 million</td>
</tr>
</tbody>
</table>

These goals include a 25% reduction in global dengue incidence by 2030 (based on reported cases (ref figure), 2010 – 2020 as baseline). The widescale adoption of novel interventions is expected to make the largest contribution to this proposed reduction. Despite being one of the most promising novel interventions, *Wolbachia* replacement methods remain one part of wider innovations in vector control which, itself, is one part of a wider control strategy also including new therapeutics and vaccines. Nonetheless, such goals are useful for understanding the scale at which *Wolbachia* will need to be implemented to contribute to this global goal and country-specific dengue goals. As transition to scale has been a key challenge for the replacement method, a model was developed to quantify the scale necessary for such a method to contribute substantially to the WHO dengue reduction goals.

**Data used for the model**

*Baseline dengue burden*

A 5km x 5km map of dengue burden was obtained from the Bhatt et al. 2013 study.\textsuperscript{18} This estimates the spatial distribution of the 96 (67 – 196) million symptomatic cases that they estimate to occur each year. Because many of these cases do not seek treatment or are not diagnosed or reported, this estimate is much higher than officially reported cases. However, it is necessary to have a globally consistent and comprehensive estimate of burden that can be disaggregated to the kinds of scales in which replacement methods would be implemented. The 95% credible intervals of the burden estimate were also used to propagate burden uncertainty through the analysis.

*Cost per dengue case*

An average direct medical cost per symptomatic case (2013 USD) was derived for each country from the Shepard et al. 2016 study,\textsuperscript{19} considering the different costs


of hospitalized and ambulatory cases and the proportion of total symptomatic cases that they account for. Direct medical costs include the costs of specific medicines and staff time required to treat a dengue patient and a portion of infrastructural costs and is the most relevant measure of what governments need to pay to treat cases of dengue illness each year. All costs were inflated from 2013 to 2020 USD using World Bank country GDP deflators with a maximum cap value of 2-fold.\(^{20}\)

**Cost of preventive and reactive vector control for dengue**

A literature review on the cost of vector control in dengue endemic countries was conducted and identified studies with national and subnational estimates of vector control costs for 17 countries. Twenty studies included costs of routine vector control activities and seven studies included costs of vector control during dengue outbreaks. All vector control cost values were converted back to local currencies using the exchange rate at the time of the costing, these local currency values were inflated to 2020 using country GDP deflators published by the World Bank,\(^{21}\) and inflated local currency values were converted to 2020 US dollars using 2020 exchange rates published by the World Bank.\(^{22}\)

To make predictions of per capita routine vector control costs for countries without costing data, a Poisson generalized mixed linear model was fit to the costing data with national GDP per capita (log scale) as a covariate and national-level random effects. The final model explained 88% of the deviance in the data. The addition of estimated hospitalized dengue case costs and continent as further covariates were considered, but only explained < 1% additional deviance. Predictions were then made for all countries globally using World Bank GDP per capita figures from 2020. For countries where this data was missing (some small Caribbean and Pacific island nations), global median GDP per capita was assumed.

Of the seven studies identified that included costs of vector control during dengue outbreaks, five studies gathered information on both routine and outbreak vector control activities. It is expected that implementing a *Wolbachia* release program will not avert routine vector control costs because *Wolbachia* replacement is unlikely to eliminate dengue in most settings and additional vectors (e.g., *Aedes albopictus*) and nuisance biting mosquitoes will still drive a need for routine vector control activities. Instead, it was assumed that the implementation of *Wolbachia* replacement will significantly limit the size of outbreaks and their required vector control response. It was therefore assumed that these outbreak vector control costs are avertable post *Wolbachia* replacement. These studies suggested that during outbreaks, the monthly cost of vector control increases by 20-50%. Three scenarios were explored where additional avertable outbreak costs composed 35% of routine monthly costs for a duration of 3 months, with a sensitivity analysis where 20 or 50% values were applied to lower or higher burden estimate 95% credible intervals respectively.

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20 GDP Deflation Index data for each country from: https://data.worldbank.org/indicator/NY.GDP.DEFL.ZS
21 GDP Deflation Index data for each country from: https://data.worldbank.org/indicator/NY.GDP.DEFL.ZS
22 Exchange rate data for each country from: https://data.worldbank.org/indicator/PA.NUS.FCRF
**Effectiveness of replacement programs**

Only one randomized controlled trial has been conducted for the replacement method with epidemiological endpoints, to date, which found a 77% reduction in dengue incidence in Yogyakarta, Indonesia\(^{23}\) following the implementation of wMel Wolbachia by WMP. It is expected that alternative replacement products should have effectiveness not substantially worse than this in the equivalent urban and dengue transmission environments. However, it is expected that effectiveness will be reduced in high transmission environments.\(^ {24}\) A conservative global average effectiveness of 70% was therefore assumed for municipal Wolbachia replacement campaigns. Tests of 3-, 5- and 10-year scenarios for duration of effectiveness were tested, with financial benefits of averted case costs outbreak vector control costs and insecticide costs discounted at 3% per annum.

**Identifying areas needed to meet global targets**

First, 5km x 5km pixels were ranked by benefit-to-cost ratio (direct medical costs of averted cases and averted outbreak vector control costs over 10 years / cost of program implementation) to identify which pixels are most cost efficient for replacement. Starting with the most cost efficient, pixels were then assigned Wolbachia treatment sequentially until the cumulative averted cases exceeded 12.5% (half contribution) or 25% (full contribution) of the global burden.

**Identifying cost targets**

Determination of a price point / cost target considered multiple options, including (a) cost in relation to averted medical costs, (b) cost in relation to averted medical plus societal costs, (c) costs in relation to averted mosquito control costs, (d) costs in relation to averted emergency mosquito control costs, and (e) costs in relation to averted insecticide costs. In the absence of data on “Willingness to pay”, it was assumed option (a) + (d), i.e., averted direct medical cost of treating dengue cases and averted emergency mosquito control costs, was judged to be most predictive of actual willingness to pay as it most closely aligns with the year-to-year cost to governments of treating dengue cases and is more likely to result in net savings compared to mosquito control costs (c and e) that will still be necessary for other mosquito species. The analysis, therefore, considered at what price a hypothetical replacement program would be cost neutral or cost saving to the government in all applicable countries, i.e., the costs of the intervention are repaid over 3, 5, or 10-year time horizons after replacement with Wolbachia is complete. This cost was calculated within each of the 5km x 5km release areas necessary to meet the WHO global targets (see discussion immediately below) and expressed as a cost per person protected within each such release area.

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Scenarios for targeting areas with replacement programs to meet the WHO goals.

Scenario A: This model suggests that targeting replacement programs to a relatively small number of dengue endemic towns and cities with 70% effectiveness in implemented areas could achieve the global target of a 25% reduction in incidence. These target areas only account for 1.7% of the area at risk of dengue transmission globally and only 34.7% of the more developed, more populated areas (i.e., > 300 people per km²) at risk. Combined they span 924,557km², across 73 countries. If only half of the WHO goal is to be achieved by replacement methods, then only 255,459km² would be needed over 47 countries. This approach would, however, involve “cherry picking” certain countries with prioritization of high- and middle-income, highly dengue endemic countries over lower income, lower burden countries.

Figure 1: 5km x 5km areas where it would be most cost efficient to target replacement programs to achieve a 25% (upper) or 12.5% (lower) global burden reduction:
Scenario B: A second, more challenging optimal target was considered where a 25% reduction also needs to be achieved at the national level in the majority (95%) of dengue endemic countries. For purposes of this analysis, countries were considered dengue endemic if they were estimated to have >10,000 symptomatic dengue infections a year.

3. **Identify Wolbachia replacement cost targets to meet WHO dengue reduction goals.**

Given the assumption that (i) a *Wolbachia* replacement program should be cost neutral from the government perspective (based on averted case and outbreak vector control costs), and (ii) *Wolbachia* replacement programs should be developed with the intention of having significant impact toward achieving WHO dengue reduction goals, the model can be used to estimate the target cost that will need to be achieved in order to meet the WHO global goal or the same goal at a national level (Table 1, below) in each and every 5km x 5km area that needs to be treated to achieve the stated goal. The replacement program must therefore have a cost that is equal to or less than the lowest cost area in which it needs to be deployed. This modelling framework and preliminary results give a template for how efficacy and cost efficacy could be approached for the TPP and give an approximation of the targets that may be considered. With respect to these cost targets, it should be noted:

The cost targets shown in the table below represent the cost required for a *Wolbachia* replacement program to be at least cost neutral in every target area. This cost, therefore, represents the area with the lowest avertable dengue costs within the global (A) and national (B) reduction scenarios and is the least cost-efficient area to implement a *Wolbachia* program. Thus, these areas require the lowest *Wolbachia* program cost. Replacement programs could have higher, and in some cases substantially higher, costs in many other target areas and still be cost neutral with areas that have high dengue burden and high cost of case treatment and prevention supporting higher *Wolbachia* program costs. However, in order to reach enough areas to have a large enough impact on the global and national burden the program must be able to achieve the cost targets in the least cost efficient target area to ensure it is suitable for all target areas.

- These projected cost targets make no assumptions about how replacement of *Wolbachia* is achieved and therefore do not consider any of the additional programmatic challenges that might increase cost of *Wolbachia* replacement implementation in some areas (e.g., high population density, inaccessible local topography, first deployment in the setting or “follow on” deployments). The estimated costs merely identify what cost per person would be justifiable in each area, leaving programmatic innovation and pricing structures as potential solutions to overcome these challenges.

In this analysis each 5 x 5km area is treated independently. In reality, the cost of implementation is expected to be lower if previous programs, particularly in the same country, have established the infrastructure and expertise that could be re-used for subsequent releases. Practically this may mean that high burden areas that can support higher *Wolbachia* program costs could be implemented first with the less
cost-efficient areas treated last once all appropriate rear and release infrastructure has been established. These cost targets therefore represent the mature cost of the intervention and earlier program costs may be substantially higher.

Table 1: The model-predicted cost (per person covered) target for a *Wolbachia* replacement program if it is to have a sizeable impact on global dengue burden. These targets assume the program is at least cost neutral, i.e., implementation cost is less than or equal to the direct medical costs of averted cases plus vector control outbreak costs. These targets represent the cost at which implementation would be at least cost neutral in all needed areas to meet the stated burden reduction targets, but many areas within this could support a higher cost due to higher direct medical costs. All values 2020 US dollars, brackets show model predicted uncertainty around the true value of this cost threshold at the 95% credible interval level):

<table>
<thead>
<tr>
<th></th>
<th>Cost of the program needed per person covered with 10 years benefits</th>
<th>Cost of the program needed per person covered with 5 years benefits</th>
<th>Cost of the program needed per person covered with 3 years benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>To achieve a 12.5% global burden reduction</td>
<td>$7.63 (5.15 - 29.42)</td>
<td>$4.10 (2.77 – 15.83)</td>
<td>$2.54 (1.71 – 9.78)</td>
</tr>
<tr>
<td>To achieve a 25% global burden reduction</td>
<td>$4.33 (2.73 – 18.95)</td>
<td>$2.33 (1.47 – 10.20)</td>
<td>$1.44 (0.91 – 6.30)</td>
</tr>
<tr>
<td>To achieve a 12.5% burden reduction on a national basis</td>
<td>$0.98 (0.64 – 3.78)</td>
<td>$0.53 (0.34 – 2.03)</td>
<td>$0.33 (0.21 – 1.26)</td>
</tr>
<tr>
<td>To achieve a 25% burden reduction on a national basis</td>
<td>$0.72 (0.26 – 1.66)</td>
<td>$0.39 (0.14 – 0.89)</td>
<td>$0.24 (0.09 – 0.55)</td>
</tr>
</tbody>
</table>

Table 2: As table 1, but assuming the cost of implementation is less than or equal to vector control outbreak costs only.

<table>
<thead>
<tr>
<th></th>
<th>Cost of the program needed per person covered with 10 years benefits</th>
<th>Cost of the program needed per person covered with 5 years benefits</th>
<th>Cost of the program needed per person covered with 3 years benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>To achieve a 12.5% global burden reduction</td>
<td>$0.50 (0.19 – 0.96)</td>
<td>$0.27 (0.10 – 0.52)</td>
<td>$0.17 (0.06 – 0.32)</td>
</tr>
<tr>
<td>To achieve a 25% global burden reduction</td>
<td>$0.28 (0.14 – 0.72)</td>
<td>$0.15 (0.08 – 0.39)</td>
<td>$0.09 (0.05 – 0.24)</td>
</tr>
</tbody>
</table>

25 These “intervention benefits” might best be expressed as (direct medical costs of averted cases over [x] years + averted emergency vector control costs over [x] years / cost of program implementation).

26 These values express model-based uncertainty around the true value of the cost target. They do not represent a range of costs and do not and should not be seen or used as such by manufacturers, implementers, or programs.

27 National level in the majority (95%) of dengue endemic countries. For purposes of this analysis, countries were considered dengue endemic if they were estimated to have >10,000 symptomatic dengue infections a year.
4. **Identify and compare potential costs of various deployment/implementation models:**

Using this modelling framework, it is also possible to consider various deployment and implementation options, related to (i) releases themselves and the mechanics involved, and technology used, in releases, and (ii) the overall structure and participants in a full *Wolbachia* replacement program. With respect to releases, it is anticipated that releases will be through the field distribution of so-called mosquito release containers (MRCs) which are ready to distribute containers that house eggs. This has been the approach increasingly/predominantly used by WMP in their most recent and largest deployments and by Oxitec with respect to their “friendly mosquito” suppression program. It has many benefits, including the fact that it standardizes and simplifies dramatically the logistics of releases and the technical expertise required for releases.

There are two models emerging for the conduct of *Wolbachia* replacement programs. The first is a turnkey model, where the manufacturer is directly responsible for all aspects of rearing, set-up (including community engagement and release design/planning), release, and post-release monitoring. The second can be termed an “integrated model,” where the manufacturer (either locally or via regional or global rearing and release facilities) supplies ready-to-distribute MRCs and another organization (typically local vector control staff or a local community organization) handles all aspects of set-up, release, and monitoring. Initial model results suggest that an integrated model that fully leverages existing supply chains and resources (with no net increase over existing control program costs – which may be somewhat unrealistic at least initially given the significant differences between traditional vector control activities and *Wolbachia* replacement method deployments) could result in a ~ 81% (range 90 – 56%) reduction in replacement program costs compared to the turnkey model (which offers no additional savings in existing control program costs). It is also noted that there may be a third model, where a first in-country deployment might be turnkey and that such an initial deployment would include intensive training of local distribution or implementation partners in the unique requirements of *Wolbachia* replacement method deployments. Thereafter, additional in-country deployments might be shifted from a turnkey to an integrated model. Further understanding and encouragement of these integrated models seems critical, in that such a model may increase the likelihood of per person covered cost targets being achieved because there are natural synergies obtained from leveraging existing vector control resources, infrastructure, and supply chains.

The TPP must, however, allow flexibility in implementation approaches and must acknowledge that countries have very different levels of expertise and experience in their vector control programmes. While more integrated implementation models may appear to have lower overall costs, such considerations should be secondary to effectiveness.

5. **Seek Also to Identify a “Product” Cost.** Recognizing that the TPP should anticipate and allow flexibility in implementation approaches and should also acknowledge that countries have very different levels of expertise, experience, resources, and infrastructure in their vector control programmes, cost targets that support both implementation models can and should be established. In other words, cost targets for BOTH the turnkey
implementation approach and the integrated implementation approach (as defined above) should be developed. The model establishes cost targets ("Total Cost of Coverage") that need to include all the activities and costs required to achieve "target coverage" (the proportion of the local Aedes aegypti population that has Wolbachia that is deemed necessary to achieve Wolbachia replacement method efficacy). Analysis of previous release budget items from early phase replacement programs suggest that, on average, 18.6 percent (range 10.1% – 44.3%) of the Total Cost of Coverage is directly related to production – to creating the ready-to-distribute "MRCs" described above (i.e., product costs). Budget items included in these product costs (this 18.6% average) include facility set-up, mosquito line creation, rearing diagnostics and a portion of overheads, administration, and management costs. As indicated by the range, these product costs will vary considerably, depending among other things on whether new facility and equipment are required (as with first deployments) or whether existing facility and equipment can be leveraged (as in follow on deployments). By applying this product cost average to our modelled Total Cost of Coverage targets, a “target product cost” for each of scenarios included in Table 1 and Table 2 above can be generated (by multiplying each figure by 0.186). This approach assumes that future innovations to reduce the cost of Wolbachia programs act evenly on all aspects of the program (production, community engagement, release, etc) and that the proportional cost of each aspect remains unaffected. Combining these two analyses also means that this derived product cost inherits all the same assumptions and caveats of the previous analysis. In particular, this derived target product cost is the mature product cost in later phases of release once deployed at scales capable of having a substantial impact on the global burden of dengue. Nonetheless, this calculated target “product” cost is useful in both optimizing production and product innovation and in permitting programs to evaluate turnkey versus integrated approaches to Wolbachia replacement implementations.

**Conclusion – Regarding Wolbachia Replacement Method TPP and Hybrid Model PPC Development.**

This document has highlighted and quantified some of the challenges associated with bringing the proven-effective Wolbachia replacement technology to levels of non-donor funded scale-up required to meaningfully impact dengue incidence and move toward the achievement of WHO dengue targets. As indicated in the Terms of Reference for the TAG, “... the groundwork has been laid for a global effort to use Wolbachia to control /eliminate dengue. To ensure appropriateness, accessibility, affordability and acceptability of this technology, it is essential that the global community define the use case(s) and develop a Target Product Profile (TPP). The quantified targets in the TPP will enable a gap analysis with respect to available technologies and help to drive further innovation and to identify the circumstances where the technologies should be targeted.”

As the TAG considers these issues of appropriateness, accessibility, affordability and acceptability and establishes quantifiable TPP targets, the modelling and other information highlighted herein and to be covered in some more detail during the meetings, is intended to help the TAG ascertain and promulgate suitably and sufficiently aggressive efficacy, cost-efficacy, and other targets.

Under its Terms of Reference, the TAG also is asked to consider potential combination(s) of Wolbachia Aedes aegypti population replacement product/approach and/or other Aedes aegypti population

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28 Call for experts: Technical Advisory Group (TAG) on the Development of a TPP for a Wolbachia spp. strain (Aedes aegypti population replacement product)
suppression products/approaches (based on Wolbachia or other technologies), after development of the Wolbachia Aedes aegypti population replacement TPP. In earlier published studies, it was noted that “strategically combining the suppression methods with Wolbachia can generate a sustained control while mitigating the risks of inadvertent exacerbation of the wild mosquito population.”

In addition, in his perspectives piece, Scott Ritchie also noted: “There are two huge expenses for rear and release programmes, excluding communications: the production and release of massive numbers of mosquitoes, and monitoring. Any method that can reduce the release numbers will result in significant savings. Thus, integration with existing vector control programmes or citizen science programmes that involve source reduction to reduce wild populations, and thus required release numbers, should pay dividends.”

To date, there have not been any trials or pilots to formally evaluate the benefits and detriments of such a “hybrid” approach. It is hoped that the promulgation of a form Preferred Product Characteristics (PPC) document by the TAG will invite and encourage further investigation, collaboration, and formal evaluation of this potentially interesting and impactful approach.


Appendix

Description of *Wolbachia* Replacement Method


Our method utilises *Wolbachia*, obligate intracellular endosymbionts that are common in insect species but were not present in *Ae. aegypti* mosquitoes until they were stably transinfected in the laboratory. In insects *Wolbachia* is maternally transmitted via the egg and manipulates insect reproduction to favour its own population dissemination via cytoplasmic incompatibility (CI). The result is that *Wolbachia* rapidly enter into naïve mosquito populations in a self-sustaining, durable manner. Multiple *Ae. aegypti*: *Wolbachia* combinations have been generated by the O’Neill laboratory where they form stable, maternally-transmitted infections that cause CI. Strikingly, the presence of *Wolbachia* in *Ae. aegypti* mosquitoes renders them more resistant to disseminated arbovirus infection, including dengue, Zika, chikungunya and yellow fever viruses. Thus, the critical and signature effect of *Wolbachia* as a public health intervention is to severely reduce the vectorial capacity of mosquito populations to transmit arboviral infections between humans. For field implementation, the approach works by seeding wild mosquito populations with *Wolbachia* through controlled releases of relatively small numbers of *Wolbachia* infected mosquitoes (Figure 4). Over several months, and through the actions of CI, the prevalence of *Wolbachia* in the local mosquito population increases, until such time as the majority of mosquitoes in the area carry *Wolbachia*.

![Figure 4. The *Wolbachia* biocontrol method. *Ae. aegypti* mosquitoes with *Wolbachia* (green) are released into the wild mosquito population (black).](image)

Over a series of releases, the percentage of *Wolbachia* mosquitoes increases. Once a threshold frequency of *Wolbachia* mosquitoes is reached, *Wolbachia* will continue to spread after releases have finished until the majority of mosquitoes carry *Wolbachia*. Laboratory vector competence studies show that *Wolbachia*-infected mosquitoes have a significantly reduced ability to transmit dengue, Zika and chikungunya viruses.