Proposed Recommendations for SAGE Consideration

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SUMMARY
EPIDEMIOLOGY AND DISEASE BURDEN

Epidemiology and Disease Burden

- Increasing and substantial global burden, currently estimated to be annually:
  - 390 million infections
  - 96 million clinical infections
  - 2 million severe dengue cases
  - 20,000 deaths
- Geographic and temporal heterogeneity in disease transmission

SUMMARY
CLINICAL TRIALS EFFICACY

Vaccine Efficacy from M0-M25

- Post-hoc **pooled 9-16 years vaccine efficacy was 65.6%** (CI 60.7-69.9).
- Pooled 9-16y ITT vaccine efficacy (≥1 dose) varies by:
  - infecting **serotype**
    - **DENV-1** 58.4%, **DENV-2** 47.1%, **DENV-3** 73.6%, **DENV-4** 83.2%
  - **serostatus**
    - **seropos** 81.9%, **seroneg** 52.5%
  - **severity** of disease
    - **severe** VCD 93.2%, **hospitalised** VCD 80.8%
  - **age**
    - **CYD14** 6-11y 59.5%, 12-14y 74.4%
    - **CYD15** 9-11y 61.7%, 12-16y 67.6%
- Note correlation of serostatus and age
- Leads to variable efficacy by country.
- Protection is seen after the first dose.

VCD = virologically confirmed dengue

Longer-term Follow-up

Vaccine efficacy against VCD of any severity is not evaluable after M25, although trends in the relative risk against dengue hospitalization, when protective, approach 1 in subsequent years, suggesting waning protection.

SUMMARY
VACCINE SAFETY

Safety Assessment

- CYD-TDV is well-tolerated.
- SAEs similar across CYD/Placebo in Phase 3 trials.
- No non-dengue safety signals identified (including all-cause mortality).
- Hypothetical AND/AVD risk (under study by manufacturer).
- Limited experience so far with vaccination in pregnancy (therefore, a contraindication).
- Understanding the potential factors associated with the increased relative risk of hospitalized and severe dengue among some trial participants is a priority.

Longer-Term Follow-up – Hospitalized and Severe Dengue

Elevated risk of hospitalized and severe dengue primarily seen in 2-5 year-old age group in Year 3.

- Risk diminishes in Years 4 and 5.
- Overall excess of cases among vaccinated in 2-5 year age group, but not statistically significant.

  [58 vs 23 RR=1.26 (95% CI 0.76-2.13)]

- Elevated risks in other age groups at certain time points are found, but they are not seen consistently across the three trials.

SUMMARY
DISEASE AND ECONOMIC MODELLING

Disease Modelling Conclusions

- **Predicted impact** of vaccination programs:
  - Routine immunisation of 9+ year olds at 80% coverage predicted to reduce dengue disease by 10-30% long-term in moderate-to-high transmission settings
- **Heterogeneity, variation of vaccine efficacy with serostatus**:
  - Target age for vaccination should be tuned to setting: 9 years only optimal for highest transmission setting
  - 11-14 year olds a good compromise in moderate to high transmission settings
  - Vaccine unlikely to be beneficial in low transmission settings
- **Careful communication** required because of moderate and heterogeneous vaccine efficacy

Economic Modelling Conclusion

In most settings and for most models, the total cost of fully vaccinating one person cannot exceed $50 for the vaccine to remain cost-effective.

Modelling Cautions

Efficacy may vary by serotype:

- Seen in trial endpoints, but this may reflect differing propensity between serotypes to cause disease in primary vs secondary infection

Efficacy may vary by age:

- Seen in trial endpoints, but can largely be explained by assuming only serostatus-dependent efficacy
- But can't rule out an additional causal effect of age

These and other uncertainties may affect long term impact:

- Need long-term follow-up
- Early vaccination programmes/phase 4 trials need careful monitoring

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PROPOSED RECOMMENDATIONS

Vaccine Introduction

Countries should consider introduction of CYD-TDV in geographic settings (national or subnational) with high dengue transmission

- i.e. seroprevalence of approximately 70% or greater in the age group targeted for vaccination but not below 50%.

Robust epidemiologic data could potentially be used as a proxy for seroprevalence

Seroprevalence

- Where possible, assessment of dengue transmission intensity should be supported by geographically relevant seroprevalence studies.
- Seroprevalence estimates should guide decision-making and introduction at subnational levels while noting that these are not precise indicators.
- Work is needed to identify routinely collected epidemiologic indicators that can be used to infer likely seroprevalence.

National and Sub-National Considerations

- Decisions about introduction require careful assessment at the country level, including:
  - consideration of local priorities,
  - subnational dengue epidemiology,
  - predicted impact and cost-effectiveness with country-specific hospitalization rates and costs,
  - affordability and budget impact.

- Vaccination should be considered as an integrated strategy together with:
  - well-executed and sustained vector control
  - the best evidence-based clinical care for all patients with dengue

Vaccine Scheduling & Tracking

- CYD-TDV is recommended as a three-dose series given 6 months apart.
  - Currently there is no recommendation for a 4th dose.
- Should a vaccine dose be delayed for any reason, it is not necessary to restart the course and the next dose in the series should be administered.
- Because of the duration of the vaccine schedule and to enable better vaccine monitoring, countries should have systems in place for tracking vaccination.

Target Age

- The target age for routine vaccination should be defined by each country based on an assessment of dengue endemicity and programmatic feasibility of targeting particular ages.
- The age to target to optimize impact likely varies by transmission setting.

Age Limits for Vaccination

- No vaccination is recommended under age 9 years due to the potential safety concern signalled in children aged 2-5 years of age in the Phase 3 trial.
- Although only immunogenicity (not vaccine efficacy) has been studied in clinical trials of 17-45 year-olds, in principle, these age groups could be targeted for vaccination.
- At this stage, insufficient data are available to permit a recommendation for use above the age of 45 years.

Co-administration, Routine and Priority Use

- Co-administration is not recommended until data are available on the safety and immunogenicity of CYD-TDV when co-administered with other age-appropriate vaccines.
- CYD-TDV should be introduced as part of a routine immunization program in appropriate settings.
- Catch-up campaigns targeting priority age groups defined by local epidemiology can be considered for a greater immediate impact.

Outbreak response

- CYD-TDV should not be considered as a tool for outbreak response.

- A dengue outbreak is a signal that an improved dengue control strategy is needed.

- When an outbreak occurs in an area that meets the criteria for routine introduction in relation to transmission intensity, vaccination with the 3-dose schedule as part of an overall dengue control strategy may be considered.

Special populations – 1

- **Pregnant women**
  - CYD-TDV is contraindicated in pregnant and lactating women because insufficient data have so far been gathered on its use in pregnancy.
  - Based on limited cases arising from inadvertent pregnancies that occurred during clinical trials, there are no data to warrant termination of a pregnancy should the vaccination have occurred anytime during that pregnancy.
  - If a woman becomes pregnant before all three doses have been administered, the remaining doses should be administered after lactation.

- **Immunocompromised persons**
  - CYD-TDV is contraindicated in immunocompromised individuals. More data will be available from upcoming studies in HIV-infected individuals.

Special populations – 2

- **Travellers**
  CYD-TDV has not formally been licensed for use in travellers.
  - In travellers who have already been previously infected with dengue, vaccination for travel to high transmission settings may be beneficial.
  - Extrapolation of data from the Phase 3 trials suggests that in such persons there may be some protection after the first dose, but completion of the full 3-dose schedule is still recommended.
  - In travellers unlikely to have already had dengue, vaccination may be substantially less beneficial (and there is a theoretical risk that it may be harmful), analogous to seronegative individuals living in endemic settings.
  - Co-administration with other travel vaccines is not recommended.

- **Health care workers**
  There are no specific recommendations for health care workers.

Surveillance

- Dengue surveillance should be strengthened, particularly in the context of emerging infections with clinical similarities to dengue.
  - In areas of the world for which there is a paucity of data, further characterization of the burden of dengue, which appears to be growing, is needed.
  - Harmonized case-definitions are encouraged to enhance data sharing and comparisons across regions.
- Using surveillance data to monitor population impact of a vaccination program may be challenging as the year-to-year variability in dengue transmission may be greater than the expected vaccine impact.
  - Long-term monitoring for severe dengue in vaccinated subjects to assess long-term effects of vaccination should be done in selected areas.

Additional Preventative Measures Still Required

- Due to the partial efficacy of the vaccine against dengue of any severity, careful communication is needed to inform vaccinees that they may still be at risk of dengue and of the importance of receiving all three doses and of adhering to other disease preventive measures.
- An assessment of vaccine effectiveness, and the durability of that effectiveness, is a priority.
  - Current data suggest substantially lower benefit of vaccination in seronegative individuals 9-45 years of age.
  - There is a theoretical possibility that vaccination could do harm in this population.
  - Although theoretical risks not supported by data should not impede rollout of this vaccine, it is critical to evaluate as soon as possible whether there is any risk to this population.

Critical Research Recommendations

CYD-TDV

- Risk of severe/hospitalized dengue over time in vaccinated seronegatives
- Duration of protection/need for additional doses

Dengue Vaccine Field

- Second-generation vaccines that include characteristics such as improved protection against all four dengue serotypes, single-dose, for use in younger age groups

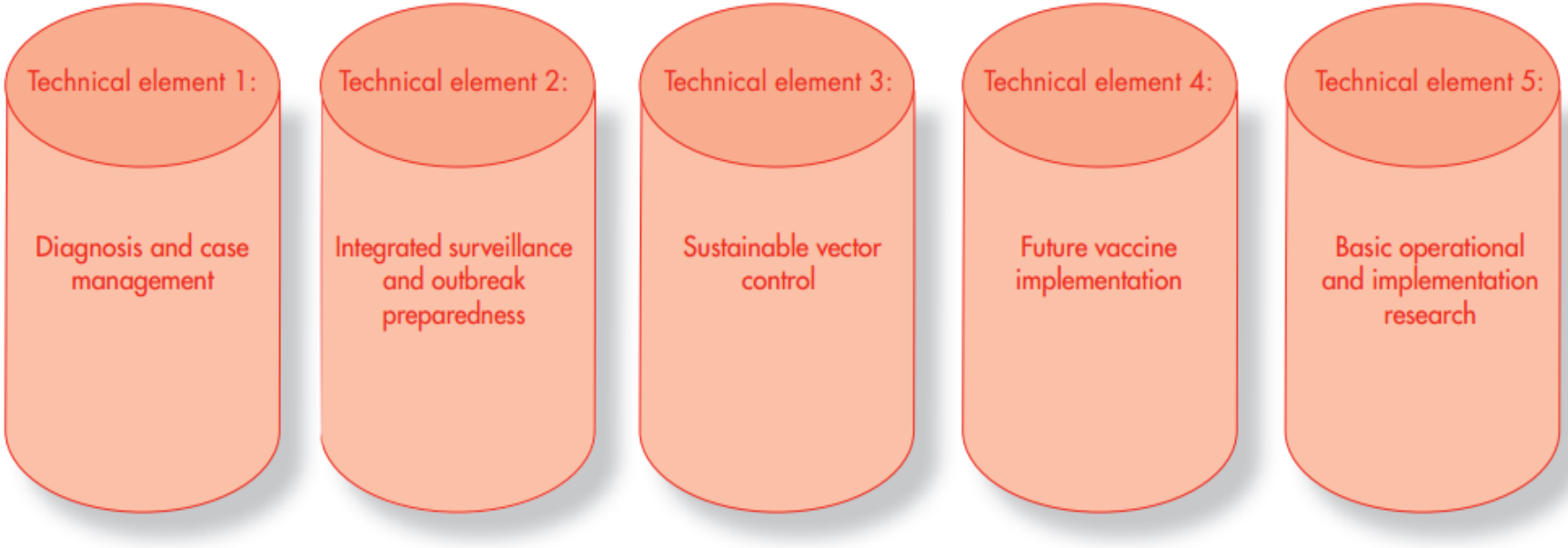
Additional high-priority research questions listed in the Background Paper

WHO Global Strategy for Dengue Prevention and Control 2012-2020

OBJECTIVES:

- To reduce dengue mortality by at least 50% by 2020*
- To reduce dengue morbidity by at least 25% by 2020*
- To estimate the true burden of the disease by 2015

* The year 2010 is used as the baseline.



ENABLING FACTORS FOR EFFECTIVE IMPLEMENTATION OF THE GLOBAL STRATEGY:

- advocacy and resource mobilization
- partnership, coordination and collaboration
- communication to achieve behavioural outcomes
- capacity-building
- monitoring and evaluation