Forecasting dengue vaccine demand in disease endemic and non-endemic countries

Ananda Amarasinghe,* Ole Wichmann, Harold S. Margolis and Richard T. Mahoney

Pediatric Dengue Vaccine Initiative (PDVI); International Vaccine Institute; Seoul, Korea

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Background: A dengue vaccine in large-scale clinical trials could be licensed in several years. We estimated the potential vaccine demand for different introduction strategies in 54 dengue-endemic countries and for travelers from non-endemic countries to enable vaccine producers and public health agencies to better prepare for timely utilization of the vaccine.

Results: Under our assumptions, 2.4–3.5 billion dengue vaccine doses would be needed in the first five years after introduction with >75% delivered in the public sector. Among 20 potential ‘early-adopter’ countries, an estimated 0.9–1.4 billion doses would be needed for the same introduction approach. For the private sector, covering 10% of children and 30% of adults an estimated 443–664 million doses would be required. In non-endemic countries, travelers could use an estimated 59–89 million vaccine doses, although the present product profile would make it unlikely to be able to administer vaccine in a timely manner.

Methods: Calculations were based on 2015–2020 population projections for endemic countries in Asia and the Americas with populations >100,000. For dengue-endemic countries we assumed country-wide routine 12–23 month-old vaccination and catch-up vaccination among 2–14 year-old children employing a 2 or 3-dose schedule. Assumptions on expected vaccination coverage were based on country-specific public, private and travelers’ sectors immunization performance.

Conclusions: Our results project an upper-limit estimate of vaccine demand, with actual demand depending on country priorities, cost and product profile. Given the potential for a dengue vaccine, policymakers in endemic and non-endemic countries should consider appropriate implementation strategies in advance of licensure.

Introduction

Dengue is a mosquito-borne, emerging viral disease of humans, with about 55% of the world’s population living in areas where dengue virus (DENV) transmission can occur.¹ The disease is endemic in tropical and sub-tropical areas of Asia, the Americas and the western Pacific. Annually, there are an estimated 50 to 100 million DENV infections with about 500,000 requiring hospitalization due to development of dengue hemorrhagic fever (DHF).^{2,3} Several vaccine candidates are under development and four have entered clinical trials,^{4,5} including one in a large-scale efficacy trial. A safe and effective dengue vaccine might be available for introduction in public health programs within the next 4–5 years.

In dengue non-endemic countries, dengue is common among travelers.⁶ Among travelers reported by the GeoSentinel surveillance network, dengue was the leading cause of febrile illness among those with a specific diagnosis returning from every geographic region except sub-Saharan Africa and Central America.⁷ Although most DENV infections in travelers are mild, severe disease has been increasingly described, including hemorrhage, shock and death from intracranial hemorrhage or fulminant hepatitis.^{8–12}

To begin to understand the potential markets for a safe and effective dengue vaccine and to support vaccine manufacturers and governments in their preparation for vaccine introduction, we estimated the potential vaccine volume demand for the public and private sectors in disease endemic countries and of the travelers market in non-endemic countries. These estimates should aid in determining vaccine production requirements and planning for the financial and logistical support required for vaccine introduction. Since it is still early in the evaluation of dengue vaccine efficacy and dosing, the price per dose cannot be established and our estimates are in volume (vaccine doses) and not monetary value. Our analytic horizon was limited to vaccine introduction during the first 5 years after availability of a licensed product.

Results

Potential volume demand—endemic countries. *Population at risk and birth cohort size.* Fifty-four countries of >100,000 population were classified as dengue-endemic with an estimated 2015 population of 2.8 billion (Table 1). Of these, 21 (40%) were classified as GAVI-eligible with a total populations of about 1.8 billion.

*Correspondence to: Ananda Amarasinghe; Email: ana.amarasinghe@pdvi.org

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Table 1. Estimated target population (in millions) for public sector vaccination programs in 2015, by GAVI vaccine purchase category, dengue endemic countries with a population >100,000

Dengue-endemic countries—eligibility for GAVI vaccine purchase and income category*	Estimated population in 2015	Routine early childhood vaccination	Catch-up immunization	
		12 to 23 month-old cohort	2 to 4 year-old option	2 to 14 year-old option
Eligible (n = 21)				
Low income (n = 8)	411.6	8.7	23.1	103.6
Low-middle income (n = 12)	1425.0	27.3	82.5	353.4
Upper-middle income (n = 1)	11.6	0.1	0.4	1.7
Sub-total	1848.2	36.1	106.0	458.7
Not Eligible (n = 33)				
Low-middle income (n = 13)	424.6	6.6	22.9	90.7
Upper-middle income (n = 11)	530.3	9.6	26.4	118.3
High income (n = 9)	43.1	0.4	1.3	5.6
Sub-total	998.0	16.6	50.6	214.6
Total population	2,846.2	52.7	156.6	673.3

GAVI, Global Alliance for Vaccines and Immunization. *Income category according to World Bank, 2008.⁴¹ **GAVI Eligible countries:** Low income (Afghanistan, Bangladesh, Cambodia, Haiti, Lao PDR, Myanmar, Nepal, Vietnam), **Low-middle income** (Bolivia, Guyana, Honduras, India, Indonesia, Kiribati, Nicaragua, Pakistan, Papua New Guinea, Solomon Islands, Sri Lanka, Timor Leste), **Upper middle income** (Cuba). **GAVI Not-Eligible countries:** **Low-middle income** (Belize, ^{††}China, Ecuador, El Salvador, Micronesia, Guatemala, Maldives, Paraguay, Philippines, Samoa, Thailand, Tonga, Vanuatu), **Upper-middle income** (Argentina, Brazil, Colombia, Costa Rica, Dominican Republic, Fiji, Malaysia, Mexico, Panama, Peru, Venezuela), **High income** [Australia (North Queensland), Bahamas, Barbados, ^{††}Hong Kong-China, New Caledonia, Polynesia, Singapore, Taiwan, Trinidad and Tobago, [†]US dengue endemic areas]. [†]US national immunization program: Guam, Northern Mariana Island, Puerto Rico, Samoa Virgin Islands. ^{††}Counted as one country.

The 2015 estimated surviving annual birth cohort for dengue-endemic countries is 53 million, the population targeted for early childhood vaccination within the Expanded Program on Immunization (EPI). The estimated surviving 2–4 year-old and 2–14 year-old populations targeted for catch-up vaccination are 157 million and 673 million, respectively (Table 1).

Public sector demand: upper-limit estimate. Assuming a global recommendation for dengue vaccination in disease-endemic countries, an estimated 440 (2-dose schedule) to 645 million (3-dose schedule) vaccine doses would be needed in the first five years for routine early childhood vaccination within EPI programs. Highest demand would occur in LMI countries (Table 2) with 60% of doses required for GAVI eligible countries (Table 2). For catch-up immunization, the demand could be as high as 2.1 billion doses in the first five years for the 2–14 year age group, assuming a 3-dose vaccination schedule and GAVI-eligible countries would account for 68% of doses (Table 2). Approximately 15% of total vaccine volume demand of both routine early childhood vaccination and catch-up immunization are derived from LI countries, all being eligible for GAVI-support. In all these estimates, vaccine wastage was accounted as 25%. If vaccine wastage could be minimized to 10% the estimated vaccine volume would be lowered by 20%.

Public sector demand: early-adopter countries. Twenty countries were classified as potential early adopters, nine in the Americas and Caribbean and eleven in the Asia-Pacific region (Table 3). Of these, 14 belonged to the UMI and HI categories and only three were GAVI-eligible. An estimated 125 to 187 million vaccine doses over 5 years would be required for routine early childhood vaccination based on 25% wastage and a 2 or 3 dose schedule,

respectively. If wastage was as low as 10% these estimates would be lowered to 105 to 157 million doses. Over the same period, 78 to 111 million doses would be needed for catch-up vaccination of the 2–4 year age-group using a 2 or 3 dose schedule, respectively, while 347 to 490 million doses would be needed in a 2- or 3-dose schedule with 25% wastage, respectively, for immunization of the 2–14 age group (Table 3).

Private sector demand: dengue-endemic countries. The estimated 1–49 year old population in 2015–2020 residing in dengue endemic countries of Asia and the Americas is shown in Table 4 stratified by age-group, urban and rural residency and income-level; 80% of the 2.2 billion at-risk population is in Asia. Approximately, 60% of the target population lives in 13 LMI countries of Asia, which include India, Indonesia, Pakistan and the Philippines and approximately 45% of the total target population lives in urban areas (Table 4).

Based on population data and on what is known about private sector vaccine markets in developing countries (see section 2.4), we estimate that 321 to 481 million doses might be required in Asia for a 2- or 3-dose schedule, respectively, while in the Americas 122 to 183 million doses might be required for a 2- or 3-dose schedule, respectively (Table 5). Our calculations show that the highest volume demand will occur in LMI countries of Asia, mainly among individuals 15–49 years of age, followed by UMI countries in Americas.

Potential volume demand—travelers in non-endemic countries. An estimated >53 million travelers from dengue non-endemic countries arrived in the 21 most popular dengue-endemic tourist destinations each year during 2006–2007. Of these, 41% were from North America (USA, Canada), 28% were

Table 2. Estimated vaccine doses (millions) required for routine early childhood and catch-up vaccination, dengue-endemic countries, public-sector, 5-year period after licensure

Dengue-endemic countries— eligibility for GAVI vaccine purchase and income category*	Routine early childhood (12–23 months)**		Catch-up immunization			
			2–4 year-old cohort		2–14 year-old cohort	
	2-dose schedule	3-dose schedule	2 dose schedule	3 dose schedule	2 dose schedule	3 dose schedule
GAVI-eligible countries (n = 21)*						
Low income (n = 8)	73.5	108.5	52.1	73.6	234.3	330.8
Low-middle income (n = 12)	201.9	290.3	186.5	263.3	799.1	1,128.2
Upper-middle income (n = 1)	1.3	1.9	0.8	1.2	3.9	5.5
Sub-total	276.7	400.7	239.4	338.1	1,037.3	1,464.5
GAVI non-eligible countries (n = 33)*						
Low-middle income (n = 13)	64.7	96.5	51.9	73.2	205.1	289.6
Upper-middle income (n = 11)	95.4	142.1	59.7	84.3	267.4	377.5
High income (n = 9)	4.1	6.1	2.9	4.1	12.7	17.9
Sub-total	164.2	244.7	114.5	161.6	485.2	685.0
Total doses	440.9	645.4	353.9	499.7	1,522.5	2,149.5

GAVI, Global Alliance for Vaccines and Immunization. *Income category according to World Bank.⁴¹** Assumes integration into national immunization program and Expanded Program on Immunization.

Table 3. Estimated vaccine doses (millions) required for routine early childhood and catch-up vaccination, early-adopter countries*, public-sector, 5-year period after licensure

Country category**	Routine early childhood (12–23 months)		Catch-up immunization			
	2 doses schedule	3 doses schedule	2–4 year old cohort		2–14 year old cohort	
			2 doses schedule	3 doses schedule	2 doses schedule	3 doses schedule
Low-middle income (n = 6)	32–38	47–57	22–26	31–37	86–110	121–156
Upper-middle income (n = 9)	72–86	107–128	43–52	61–73	181–233	254–329
High income (n = 5)	1.0–1.1	1.6–1.7	0.8–1.0	1.1–1.4	3.1–3.9	4.3–5.6
Total doses (in millions)	105–125	156–187	66–79	93–111	270–347	380–490

Ranges are for 10% and 25% wastage assumptions, respectively. *Early-adopter countries: Low-middle income countries: Federated States of Micronesia, Nicaragua, Philippines, Sri Lanka, Thailand, Tonga. Upper-middle income countries: Argentina, Brazil, Colombia, Costa Rica, Cuba, Fiji, Malaysia, Mexico, Panama. High-income countries: New Caledonia, North Queensland, Polynesia, Singapore, US EPI covered areas. **Income category according to World Bank.⁴¹

from Europe and 23% were from three non-endemic Asian countries (Japan, South Korea, mainland China) (Table 6).

We estimated that that within the first 5 years after licensure 59 million to 89 million vaccine doses would be needed for the travelers market for a 2- or 3-dose schedule, respectively. We estimated that the highest demand (44% of the total) would occur in the European travelers market because of their higher vaccination coverage for currently available travel vaccines (Table 6).

Discussion

The geographic distribution of dengue would result in a large number of vaccine doses required for vaccination programs during the first five years after licensure and highest volume demand would occur in public sector immunization programs of LMI countries. Although there are only 21 dengue-endemic countries

in Asia and the Americas eligible for GAVI support, 65% of persons at risk for dengue (i.e., 1.8 billion by 2015) live in these countries.

Our upper-limit projections for public-sector vaccine demand are based on demographic, epidemiologic and vaccine uptake assumptions, including the rapid adoption and introduction of a global recommendation for vaccination in the 55 dengue-endemic countries. However, these upper-limit projections should be considered optimistic since no vaccine in recent history has experienced such a widespread adoption rate for reasons that include delays in country licensure, lack of National Immunization Program (NIP) infrastructure to incorporate a new vaccine and lack of vaccine financing. This is especially true for LI countries. Despite recommendations from global multi-lateral agencies and funding through GAVI, the use of HB and Hib vaccines is not universal decades after being available.^{13,14} We used factors that

Table 4. Estimated total population (thousands) of people 1–49 years of age living in dengue-endemic countries in 2015 by age-group, residency and country income category

Geographic regions by country category*	Urban		Rural		Total population aged 1–49 years
	1–14 yrs	15–49 yrs	1–14 yrs	15–49 yrs	
The Americas & Caribbean					
High income (n = 4)	956	1,807	435	964	4,162
Upper-middle income (n = 10)	99,606	222,655	22,049	49,351	393,661
Low middle income (n = 9)	13,070	22,850	9,276	15,900	61,096
Low income (n = 1)	1,543	2,500	1,741	2,820	8,604
Asia-Pacific					
High income (n = 5)	4,601	18,730	13	48	23,392
Upper-middle income (n = 2)	5,700	10,881	2,324	4,434	23,339
Low middle income (n = 16)	167,559	347,424	288,194	595,248	1,398,425
Low income (n = 7)	28,918	58,738	80,097	159,825	327,579
Total	321,953	685,585	404,129	828,590	2,240,257

*Income category according to World Bank.⁴¹

Table 5. Estimated vaccine doses (thousands) for the private sector market, dengue-endemic countries, 5 year period after licensure

Age-groups, residency and country income category*	2 Dose Schedule		3 Dose Schedule	
	Asia-Pacific	America & Caribbean	Asia-Pacific	America & Caribbean
High Income Country				
Urban Age 1–14 yrs	920.4	109.1	1,380.6	286.7
15–49 yrs	11,238.5	722.8	16,857.7	1,084.3
Rural Age 1–14 yrs	1.3	43.4	1.9	65.2
15–49 yrs	14.5	192.8.3	21.7	289.1
Sub Total	12,174.7	1,150.1	18,261.9	1,725.3
Upper Middle Income Country				
Urban Age 1–14 yrs	1,140.1	18,369.5	1,710.1	27,554.2
15–49 yrs	6,528.7	82,148.9	9,793.1	123,223.4
Rural Age 1–14 yrs	232.5	1,966.6	348.7	2,949.9
15–49 yrs	1,330.4	8,813.2	1,995.6	13,219.9
Sub Total	9,231.7	111,298.2	13,847.5	166,947.4
Lower Middle Income Country				
Urban Age 1–14 yrs	16,755.9	1,318.3	25,133.9	1,977.4
15–49 yrs	104,227.5	4,606.9	156,341.2	6,910.4
Rural Age 1–14 yrs	17,291.6	556.6	25,937.5	834.9
15–49 yrs	107,144.7	1,908.1	160,717.1	2,862.2
Sub Total	245,419.7	8,389.9	368,129.7	12,584.9
Low Income Country				
Urban Age 1–14 yrs	2,891.8	154.4	4,337.7	231.6
15–49 yrs	17,621.9	500.2	26,432.9	750.3
Rural Age 1–14 yrs	4,805.9	104.5	7,208.8	156.7
15–49 yrs	28,768.6	338.4	43,152.9	507.6
Sub Total	54,088.2	1,097.5	81,132.3	1,646.2
Total	320,914.3	121,935.7	481,371.4	182,903.8

*Income category according to World Bank.⁴¹

Table 6. Estimated number of travelers (thousands) from dengue non-endemic countries visiting the 21 most popular dengue-endemic tourist destinations and estimated number (thousands) of vaccine doses required, 5-year period after licensure

	All travelers from non-endemic areas	Travelers by residency			
		Europe	North America	Non-endemic Asia*	Other non-endemic areas**
Annual total number of travelers	53,174	15,234	22,259	12,010	3,671
Annual number of travelers requiring dengue vaccine***	30,576	8,760	12,799	6,906	2,111
Expected vaccination coverage (%)****	-	30%	15%	15%	15%
5-year demand, 2-dose schedule	59,005	26,280	19,199	10,359	3,167
5-year demand, 3-dose schedule	88,507	39,420	28,798	15,539	4,750

*Non-endemic Asian countries include Japan, South-Korea and mainland China. **Other non-endemic countries include Australia, New Zealand and the Middle East countries. ***For this calculation we used 57.5% according to reference 8 (first time + 50% of 1–3-time travel). ****Based on HAV coverage among travelers interviewed at airports.^{26,27}

Table 7. Forecast summary: Total dengue vaccine doses (millions) by market sector and vaccination schedule, 5-year period after vaccine licensure

Table 11. Breakdown summary of total dengue vaccine doses (millions), by market sector and vaccination schedule, 5-year period after vaccine licensure						
	Endemic Countries			Travelers market [D]	Total	
	Public market sector*		Private market sector [C]		All dengue endemic countries, public sector (n = 54) [A + C + D]	Early adopter countries (n = 20) [B + C + D]
	All endemic countries (n = 54) [A]	Potential early adopter countries (n = 20) [B]				
2 dose schedule	1,897	445	443	59	2,399	947
3 dose schedule	2,695	636	664	89	3,448	1,389

*Includes routine vaccination of the 12–23 month age group, and catch-up vaccination of the 2–14 year cohort. Excludes 2–14 years age-group estimates of the private sector estimates and numbers deviates therefore from those presented in Tables 2 and 3. *Public Sector vaccine wastage 25%.

influenced adoption of these two vaccines¹⁴ to categorize dengue-endemic countries into potential early or late adopters, which we believe provide more realistic vaccine demand forecasts for the first five years following initial licensure (Table 7).

Introduction of dengue vaccine will have several unique challenges. It will be one of the first vaccines introduced almost exclusively into low- and middle-income countries. In addition, controlling dengue and stopping its cyclical epidemics will require catch-up immunization as part of a comprehensive dengue immunization strategy. Thus, introduction and uptake of a dengue vaccine may not necessarily follow the trends of HB or Hib vaccines for reasons unique to the epidemiology of this disease. This is highlighted in a recent policymaker survey which suggested rapid vaccine introduction because of the perceived public health impact of dengue in many endemic countries.¹⁵ However, it is still unknown which factors, including price and other national priorities, will facilitate or hinder the actual demand for a dengue vaccine after licensure.

The role of the private sector demand for dengue vaccine is unknown and there are few studies in low- and middle-income countries to support good forecasting. Knowledge and attitudes toward dengue and dengue prevention are high in endemic countries, both among the general public and health care providers.^{15–17} Participants in a study conducted in metropolitan Manila, Philippines, were willing to pay US\$27 to US\$32 per dose for a single dengue vaccine dose.¹⁷ Demand was associated with price

per dose, duration of protection, household income and number of dengue prevention measures practiced by the respondents.¹⁷

In recent years, new vaccines were often introduced first into the private market of both developed and developing countries, which paved the way for introduction into the public sector. While it is too early to have a clear sense of dengue vaccine introduction strategies and the production capacity for the lead candidate vaccine, it is likely that a safe and effective dengue vaccine will have substantial demand in both the public and private sectors of disease endemic countries. Having an understanding of the potential demand and markets for this vaccine should inform introduction decisions and strategies.

Our estimates indicate that the public-sector market in endemic countries would be the major driver for vaccine uptake. Whether public sector immunization programs are likely to quickly introduce dengue vaccine will depend on a number of factors including national recommendations for vaccine use, NIP capacity to integrate a new vaccine into the EPI and to conduct catch-up immunization programs, burden of dengue and perception of disease importance and ability of the country to finance vaccine purchase with or without donor support.

Routine immunization of the 1–2 year-old cohort in the EPI will likely be the easiest approach. A model of dengue transmission dynamics predicted that 85% of each birth cohort would have to be immunized to stop DENV transmission in that cohort.¹⁸ However, catch-up immunization for older age-groups with high

disease burden would be essential to control dengue within a reasonable period of time, similar to what was done for measles, hepatitis A and varicella, diseases with a relatively wide age-range of affected persons.^{19–22} Country-specific disease reporting data will be the most practical way to identify age-groups for catch-up immunization and determine optimal immunization strategies. Implementation of catch-up immunization in the first years of vaccine introduction could be difficult since this vaccine delivery infrastructure does not exist in many countries and would require significant financial, logistical and human resources and may further be impeded by vaccine supply if there is limited production capacity.

The large number of persons traveling from non-endemic countries to popular tourist destinations with risk for DENV transmission could make this an attractive travelers' vaccine. However, based on the experience with hepatitis A vaccine, there would need to be a substantial increase in awareness and education to achieve appropriate vaccine coverage levels for persons at risk of dengue travelling to many tropical parts of the world.⁹ More importantly, the feasibility of achieving even modest vaccination coverage among travelers will depend on the number and time interval between doses. Initial immunogenicity data of live-attenuated dengue vaccines among persons with no previous DENV exposure shows that 3 doses are required over a 12 month period.²³ Such a schedule would limit use of this vaccine to highly selected populations of overseas workers, frequent travelers, or the military. Studies have shown that the majority of travelers seek pre-travel health advice less than 1 month before departure which makes a vaccine with 6 or even 12 months dose spacing difficult in this population.^{4,24} For these reasons, we applied a different methodology to estimate the travelers market-demand compared to the public sector, routine childhood immunization market-demand. We used a frequently used travelers' vaccine, the hepatitis A vaccine, as a proxy for vaccination coverage recognizing, that it is unknown whether a lead candidate live-attenuated vaccine can be delivered with an accelerated vaccination schedule such as it is done, with HB vaccines.²⁵ However, this may still overestimate the demand for the traveler's market.

The military in non-endemic countries might be also interested in a dengue vaccine. In East Timor in 1999–2000, 6.6% of Italian troops contracted dengue, causing half of all medical evacuations.²⁶ A recent study ranked dengue third after malaria and bacterial diarrhea as an infectious disease threat to the US military.²⁷ However, we did not attempt to estimate the potential military demand for a dengue vaccine or the demand by companies with workers in dengue endemic areas.

Limitations. Forecasting the demand years before a vaccine is licensed is limited by uncertainty around many key assumptions. This is particularly true for dengue since no other recently introduced vaccine can be used as a model from which to make the needed assumptions, particularly concerning multiple dose coverage and introduction uptake. In addition, the product profile for the lead candidate dengue vaccine (tetravalent, live-attenuated) is not fully established; recently started large-scale clinical trials should provide needed information on dose-schedule as well as efficacy and safety; factors that will have a major impact

on vaccine introduction. Single or multi-dose vial presentation will have a significant impact on vaccine wastage estimates and logistics and because the first dengue vaccines will be live-attenuated, the 'open vial policy' would not be applicable and result in higher wastage.²⁸ Further, a major factor in our analysis is the assumptions related to catch-up immunization and it is not known whether this vaccination strategy will be adopted and if adopted, how well it might be implemented.

Our estimates of dengue vaccine demand are primarily driven by two major assumptions—population at-risk of DENV infection and vaccine uptake following introduction. While we think our country-specific estimates of risk of DENV infection are robust, they are limited by not knowing the actual number of countries ready to introduce a vaccine in 2015. Factors determining the rate of introduction, which cannot be further defined at this time, include number of countries where dengue vaccine is licensed, WHO prequalification of a dengue vaccine for public sector purchase, vaccination recommendations by WHO Strategic Advisory Group of Experts (SAGE) on Immunization, country-specific vaccine recommendations and whether countries where dengue does not occur uniformly (e.g., Brazil, Mexico) would limit vaccination to populations living in selected geographical areas. Although our projections as to which countries might be 'early' or 'late' adopters of dengue vaccine use the best available predictors, they may not be pertinent to dengue vaccine.

Our estimated vaccine coverage rates were based on an imperfect model, namely measles vaccine. While we attempted to modify single dose measles vaccine coverage with drop-out rates of other vaccines, the true rates will not be known until large-scale dengue vaccine demonstration projects are implemented in some of these countries. Unfortunately, a long interval between doses is likely to increase drop-out rates. In addition, there is little experience with administration of a multi-dose vaccine to older children in catch-up immunization programs, except for measles, so these should not be considered robust estimates. Again, better estimates of complete catch-up vaccination coverage must await large-scale dengue vaccine demonstration projects in dengue endemic countries.

Another limitation is that we didn't account for the number of doses that may be needed to control dengue outbreaks. Because outbreaks are often accompanied by media attention and often cause fear in the population, this might dramatically increase vaccine demand in both the private and public sectors.¹⁵ Since there are no data from which to forecast control of dengue outbreaks through vaccination, studies will need to be conducted and policies and plans developed to handle this contingency.

The issue of vaccine safety is another limitation that could impact our estimates. Although there are theoretical concerns about dengue vaccination and the potential for immune enhanced disease related to waning antibody in persons subsequently exposed to DENV, it will take very large studies to determine if such a risk occurs.²⁹ These studies should include incompletely immunized individuals and persons at risk for inter current infections during the course of the immunization series, who may be at risk for DENV infection. However, both in vivo and in vitro studies suggest that clinically relevant antibody-dependent

enhancement of infection is unlikely to occur after vaccination against dengue.^{30,31}

Methods

Global population at risk for dengue. We defined a country as 'dengue endemic' if local transmission of DENV was officially reported in the past 10 years. We also included areas of the US with dengue and covered by their national immunization program and Australia (North Queensland) and Taiwan where dengue epidemics occurred following introductions by travelers.^{32,33} While dengue occurs in Africa, none of these countries were included because of the unknown public health impact.³⁴ We excluded dengue-endemic countries with a population of <100,000.

Our assessment was based on surviving population projections for the five year period 2015–2019, which were obtained from the US Census Bureau, except for census data obtained from India, China and northern Australia.^{35–38} For China and India we only included provinces or states where dengue has been reported. Populations were stratified by age-groups (12–23 months and 3–4, 5–9, 10–14, 15–49 years) and urban versus rural residence.

Vaccine product profile. There are four live-attenuated vaccines and one subunit vaccine in late stage development and available data indicate two or three doses would be required to achieve optimum immunogenicity; the range used in our calculations.⁴⁵ The duration of protection conferred by a dengue vaccine is unknown, but since our analysis covered only the five years after vaccine introduction, we did not account for booster doses.

Vaccine doses for dengue-endemic countries—public sector. *Demand formula and country categorization.* The following formula was used to calculate the number of dengue vaccine doses for the five year introduction period in each dengue-endemic country: n (number of doses) = (target population) $\times$ (expected coverage) $\times$ (scheduled number of doses)/(1 - wastage). We assumed vaccine will be available in single and multi-dose vials and 10% to 25% wastage, respectively, would occur in routine early childhood immunization and catch-up campaigns.³⁹ Countries were classified as eligible for vaccine purchase by the Global Alliance for Vaccine and Immunization (GAVI) using 2006 criteria and into 2008 World Bank income categories: low income (LI), low middle income (LMI), upper middle income (UMI) and high income (HI).^{40,41}

Vaccination coverage and vaccine introduction strategies. Immunogenicity data indicate that live-attenuated dengue vaccines would be administered after the first 12 months of life to avoid interference with maternal DENV antibodies.⁴² Because measles vaccine is also administered during the second year of life, we used country-specific measles vaccine coverage in 2007 as a proxy for expected dengue vaccine coverage.⁴³ We assumed an incremental increase in vaccine coverage over the five year introduction period starting with 60% of 2007 measles coverage for the first year of dengue vaccine introduction and a 10% annual increase until the 2007 measles coverage was reached in the fifth year. In addition, because vaccination coverage usually decreases between doses of multi-dose vaccines, e.g.,

diphtheria-tetanus-pertussis (DTP) or hepatitis B (HB), we used country-specific DTP coverage rates to estimate dropout from the first to the third dengue vaccine dose.⁴⁴

We assumed that the NIP of each country would implement two dengue vaccination programs, which would comprise the public sector market: (1) routine early childhood vaccination program for 12–23 month-old children; integration of vaccine into the routine EPI and (2) special catch-up vaccination programs for children ≤ 14 years of age. We considered two age groups for catch-up immunization, 2–4 year-olds or 2–14 year-olds and assumed that coverage for catch-up immunization would differ from early childhood vaccination coverage. Although measles catch-up immunization programs have reached 80–90% coverage,^{44–45} this may not be attainable for a 2–3 dose dengue vaccine regimen in older children. We assumed a 20% decline in coverage between the first to third doses in catch-up immunization programs: i.e., 90 to 70% in 2–4 year-old, 85 to 65% in 5–9 year-old and 80 to 60% in 10–14 year-old children. We assumed that catch-up immunization would be discontinued after the five-year introduction period.

Classification of early-adopter countries for dengue vaccines. Introduction rates for new vaccines into NIPs over the past decade [e.g., HB or *Haemophilus influenzae* type b (Hib)] indicate that some countries are 'early adopters' and others are 'late adopters'. We categorized dengue-endemic countries into potential early and late adopters after initial vaccine licensure based on a model that identified three factors predictive of HB and Hib vaccine uptake into NIPs: (1) general NIP performance, (2) vaccine cost relative to the country's economy and (3) perceived disease burden.¹³ For our model, we defined NIP performance as 'good' if HB or Hib vaccines were introduced before 2000 and achieved >80% coverage by 2007, or were introduced after 2000 and achieved >90% coverage by 2007.⁴³ A country was designated as an early-adaptor if its NIP performance was 'good' and it was either classified as a UMI or HI country,⁴¹ or was classified as a LMI country but reported a high perceived disease burden based on high dengue incidence or reported large dengue outbreaks.

Assessment of vaccine doses for dengue-endemic countries—private sector. In essentially all dengue-endemic countries, 85–95% of childhood vaccines are purchased and delivered through public sector programs. However, dengue affects all age-groups and demand for a dengue vaccine will not be limited to children. Since it seems unlikely that governments of affected countries can afford adult vaccination programs, we assumed that the private sector would be the major provider for adults. Due to naturally-acquired immunity in dengue-endemic countries, we assumed no demand for dengue vaccine in individuals >49 years of age. In addition, we assumed that vaccine for children would only be available in the private sector in 'late adopter' countries during the five year period after initial licensure.

Based on limited data, <10% of vaccines in low to middle income countries are purchased/delivered in the private sector. Urban areas account for a higher proportion of the market (e.g., 27% in an urban compared to 15% in a rural setting in India) and adults are more likely than children to seek vaccines in the private sector (e.g., in India 36% of women and 17% of children).^{46–48}

We assumed that in the 1–14 year-old age-group the private market share would not exceed 10%, since these age groups would be covered by the EPI and catch-up immunization programs, and that the private market in rural areas would be 50% of the market in urban areas. For UMI and HI countries we assumed the private market share to be double that for LI and LMI countries. In Asia we estimated the size of the private market penetration among adults (age 15–49) as double the private sector penetration for children. For the Americas, we estimated the market as three-fold the Asian childhood market since a higher proportion of adults are affected by dengue. Using these assumptions, the maximum penetration of the private market would be 10% and 30% in urban areas of UMI and HI countries for children and adults, respectively and 3% and 9% in rural areas of LI and LMI countries. We assume that single-dose vials would be used in the private sector with zero wastage.

Assessment of vaccine doses needed to supply the travelers market. For this market we assumed 1–3 vaccine doses to be administered over a maximum of 4 weeks; a product profile that presently does not exist. We ranked the 21 most popular dengue-endemic tourist destinations based on the number of international arrivals in Asia (Thailand, Singapore, India, Vietnam, Indonesia, Philippines, Malaysia, Cambodia, Sri Lanka) and the Americas (Mexico, Dominican Republic, Brazil, Cuba, Jamaica, Bahamas, Puerto Rico, Costa Rica, Peru, Guatemala, Colombia, El Salvador). Rankings were then adjusted by 2006–2007 international arrivals from dengue non-endemic countries using official country-specific data (Ministry of Tourism webpages). Tourist arrival data were not projected for the 2015–2020 introduction period.

Estimates of vaccine demand were derived from studies of dengue among travelers and the uptake of other travelers' vaccines. Among European travelers with dengue, 39% had traveled for the first time to a dengue-endemic country, 37% had 1–3 previous trips and 24% had >3 previous trips.⁹ Overall, we estimated that 57.5% of all travelers to disease endemic countries would be candidates for dengue vaccination; all first-time travelers should be vaccinated and 50% of persons with 1–3 previous trips and previously not vaccinated should also be vaccinated or may need a booster vaccination. We used the uptake of hepatitis A vaccine

among travelers, a vaccine that requires only one dose to be effective, to model the potential for dengue vaccination among travelers. Airport surveys in Europe and the US show hepatitis A vaccination coverage among departing travelers to the tropics of 32% and 15%, respectively.^{24,49} For travelers from Asian non-endemic countries (i.e., Japan, South Korea and mainland China) we assumed dengue vaccine coverage would be similar to hepatitis A for US travelers.

Conclusions

Despite their limitations, we believe these initial estimates of dengue vaccine demand and the different introduction scenarios provide the first step to predict production capacities for manufacturers and of vaccine availability for national policymakers and potential donor agencies. These data also provide a starting point for further models of dengue demand forecasting using different assumptions. NIP introduction strategies will be significantly impacted by the availability of an adequate supply of safe and effective dengue vaccines in the first years after initial licensure. Policymakers in endemic countries should start activities now to develop the decision-making process for dengue vaccine introduction, which would include country-level data on disease burden, cost-effectiveness of a dengue vaccine and demand forecasting.

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Author's Contributions

All listed authors made substantial contributions to conception and design of the analysis presented in this manuscript. A.A. and O.W. took lead responsibility for drafting the manuscript and R.M. and H.M. revising it critically for intellectual content. All authors read and approved the manuscript.

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