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A Model of Vaccination for Dengue in the Philippines 2016–2018

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A mathematical model of the dengue epidemic in the Philippines is developed to analyse the vaccination of children in 2016–2017. Reported case data and reported mortality data from the Philippines Department of Health is used to analyze quantitatively this vaccination program. The model compares the epidemic outcomes of no vaccination of children, vaccination only of previously infected children, and vaccination of all children.

Keywords: dengue, Philippines, vaccination, antibody, dependent, enhancement

1 INTRODUCTION

Dengue infections have increased world-wide in recent years, and dengue incidence currently affects approximately 400 million people and causes approximately 20,000 deaths each year [1]. Dengue vaccines have been developed in recent years and tested in clinical trials, and offer hope that dengue epidemics may be mitigated. A controversy, however, surrounds dengue vaccine. This controversy is associated with dengue antibody-dependent enhancement (ADE). Dengue ADE occurs after a primary dengue infection. The primary infection promotes the production of antibodies in the immune system, which are specific to the strain of the dengue virus, trap and kill this strain in the blood, and can remain in the blood for decades [2]. Dengue virus is present in four strains, and the antibodies specific to the strain of the primary infection cannot bind well with a secondary infection of a different strain. Instead, these antibodies may promote replication of a secondary infection of a different strain, with much greater disease severity than the primary strain infection.

Clinical studies have shown that dengue vaccination may mimic a primary infection, and thus promote ADE in someone who has not had a primary infection before vaccination, but has a primary infection after vaccination [3]. Clinical studies have also shown that the vaccination of someone who has previously been infected, does not have higher risk of death if a secondary infection subsequently occurs. We examine these issues surrounding dengue vaccination in the context of the dengue vaccination program in the Republic of the Philippines in 2016 and 2017.

In the Philippines, reported dengue deaths average approximately 750 people per year, with a high proportion of these deaths in younger age groups. In April 2016, the Philippines began a dengue vaccination program of 9 years old children. The program involved approximately 875,000 9 years olds, each receiving at least one dose, approximately 400,000 receiving two doses, and approximately 350,000 receiving all three doses [4, 5]. The program was terminated in December 2017, because of 12 confirmed deaths due to dengue infection of these vaccinated children [6]. As of September, 2018, 19 dengue deaths of vaccinated children had been confirmed [7]. At issue is whether these deaths were due to ADE and the failure of the vaccine to prevent a subsequent infection, and was the vaccination program justified.

In our References we have listed mathematical modelling treatments of dengue epidemics [1–5, 7, 10–23, 24–26, 34–43, 23–48, 49–55]. Our objective is to employ a mathematical model for the vaccination of a population of 875,000 9 years old children, beginning April 4, 2016 and ending

TABLE 1 | Age structured data of the dengue epidemic in years 2016, 2017, 2018. The reported data is age structured according to 5–9 or 10–14 years age brackets. The data contains no information about the effects of vaccination of this population. The data is obtained from [8] and is provided in the Supplementary Materials.

Year	2016	2017	2018
Reported cases all ages	All year = 220,518 Apr. 3–Dec. 31 = 181,000 (**Supplementary Figure S2**)	All year = 131,827 (**Supplementary Figure S4**)	All year = 216,190 Jan. 1–Sept. 30 = 163,500 (**Supplementary Figure S6**)
Reported cases ages 5 to 14	All year ≈ 89,000 Apr. 3–Dec. 31 = $\frac{181,000}{220,518} \times$ 89,000 ≈ 73,000 (**Supplementary Figure S2**)	All year ≈ 51,000 (**Supplementary Figure S4**)	all year ≈ 93,000 Jan. 1–Sept. 30 = $\frac{163,500}{216,190} \times$ 93,000 ≈ 70,300 (**Supplementary Figure S6**)
Reported infection rate of 5–14 years olds	Apr. 3–Dec. 31 $\frac{73,000}{23,000,000} \approx 0.31\%$	All year $\frac{51,000}{23,000,000} \approx 0.22\%$	Jan. 1–Sept. 30 $\frac{70,300}{23,000,000} \approx 0.30\%$
Reported case fatality rate of 5–14 years olds	All year 0.55% (**Supplementary Figure S3**)	All year 0.67% (**Supplementary Figure S5**)	all year ≈ 560 (**Supplementary Figure S7**) $\frac{560}{93,000} \approx 0.6\%$
Reported deaths ages 5–14	Apr. 3–Dec. 31 73, 000 × 0.0055 ≈ 402	All year 51, 000 × 0.0067 ≈ 342	Jan. 1–Sept. 30 70, 300 × 0.006 ≈ 422
Reported deaths all ages, all year	1,092	732	1,083

TABLE 2 | Compartments of the model.

Variable	Interpretation
S	Unvaccinated → Susceptible (without prior infection)
I_1	Unvaccinated → Infected with primary infection
I_2	Unvaccinated → Infected with secondary infection (different from primary strain)
R_1	Unvaccinated → Recovered from primary infection
R_2	Unvaccinated → Recovered from secondary infection
SV	Susceptible → Vaccinated
SVI_1	Susceptible → Vaccinated → Primary infection
SVR_1	Susceptible → Vaccinated → Recovered from first infection
SVI_2	Susceptible → Vaccinated → Recovered from first infection → Secondary infection
SVR_2	Susceptible → Vaccinated → Recovered from first infection → Secondary infection → Recovered from secondary infection
R_1V	Recovered from primary infection → Vaccinated
R_1VI_2	Recovered from primary infection → Vaccinated → Secondary infection
R_1VR_2	Recovered from primary infection → Vaccinated → Secondary infection → Recovered from secondary infection

December, 2017 (the period of the vaccination program) to provide understanding of this issue. We will use data from the Philippines Department of Health [8] to analyze the following scenarios: 1) vaccination of all the children in this population during this time period; 2) no vaccination of the children in this population during this time period; 3) vaccination only of previously infected children in this population during this time period. We will compare the numbers of reported cases and reported deaths in the first scenario with reported cases and reported deaths as projected by our model for the second and third scenarios.

2 MATERIALS AND METHODS

2.1 Data of the Epidemic

The epidemic data is from Philippines Department of Health, Epidemiology Bureau, Public Health Surveillance Division [8]. The weekly reported cases for all ages in 2016, 2017, 2018 is given in **Supplementary Figure S1** (Supplementary Materials). Reported case data for each of the years 2016, 2017, 2018 is given in the Supplementary Materials. Reported case data for 2016 is given in **Supplementary Figures S2, S3, S8**. Reported case data for 2017 is given in **Supplementary Figures S4, S5, S9**. Reported case data for 2018 is given in **Supplementary Figures S6, S7, S10**. The data in

Supplementary Figures S2–S7 is age structured according to 5 years brackets. This data does not account for asymptomatic infections nor low grade infections that are not reported. In the total Philippine population, 5–14 years olds constitute ≈23,000,000 [9]. We consider a population of 2,300,000 9 years olds in 2016, and a population of 2,300,000 8 years olds in 2016. We approximate the number of reported cases of 9 years olds in this population from April 3, 2016 to December 1, 2017, and the number of reported deaths of 9 and 10 years olds in this population from April 3, 2016 to September 30 in 2018.

In 2016, The total number of cases age 5 to 14 was 89,000 (**Supplementary Figure S2**). The total number of reported cases of ages 5 to 14 between April 3 and December 31 was $\frac{180,993}{220,518} \times 89,000 \approx 73,000$. The case fatality rate in the population of 5–14 years olds in 2016 was ≈ 0.55% (**Supplementary Figure S3**). The number of reported deaths in this population from April 3 to December 31 in 2016 is thus 73, 000 × 0.0055 ≈ 402.

Similar calculations are given for 2017 and 2018 in **Table 1**. From **Table 1** we obtain the following reported cases and reported deaths for 875,000 children who were 8 or 9 years old in 2016:

2016, April 3 to December 31: Reported cases in 437,500 9 years olds: $\frac{73,000}{10} \times \frac{437,500}{2,300,000} \approx 1,389$. Reported deaths in 437,500 9 years olds: $\frac{402}{10} \times \frac{437,500}{2,300,000} \approx 8$.

2017, all year: Reported cases in 875,000 9 and 10 years olds: $\frac{51,000}{10} \times \frac{875,000}{2,300,000} \approx 1,940$ Reported deaths in 875,000 9 and 10 years olds: $\frac{342}{10} \times \frac{875,000}{2,300,000} \approx 13$.

2018, January 1 to September 30: Reported deaths in 875,000 10 and 11 years olds: $\frac{422}{10} \times \frac{875,00}{2,300,000} \approx 16$.

Thus, 37 reported deaths occurred in reported cases from April 3, 2016 to September 30, 2018, in 875,000 children who were 8 or 9 years old in 2016, according to the reported data in [8]. Since September 30, 2018, the Republic of the Philippines Department of Public Health has not provided further information about confirmed deaths due directly to dengue infection of the 875,000 vaccinated children.

2.2 Equations of the Model

The model consists of a system of ordinary differential equations for the subpopulations of susceptible, primary infected, secondary infected, recovered from primary infection, recovered from secondary infection, unvaccinated, vaccinated without previous infection, and vaccinated with precious infection in the population of 875,000 9 years old children. We assume that the primary infection and the secondary infection correspond to two different strains of the four strains of dengue virus. We do not distinguish these four strains specifically. The model equations, with time units in weeks, are

Primary Infection

$$\frac{dS(t)}{dt} = -\alpha\Lambda(t)S(t) - \nu_S(t)S(t)$$

$$\frac{dI_1(t)}{dt} = \alpha\Lambda(t)S(t) - (\delta_1 + \beta_1)I_1(t)$$

$$\frac{dR_1(t)}{dt} = \beta_1 I_1(t) - \alpha\Lambda(t)R_1(t) - \nu_R(t)R_1(t)$$

$$\frac{dSV(t)}{dt} = (1-f)\nu_S(t)S(t) - \alpha\Lambda(t)SV(t)$$

$$\frac{dSVI_1(t)}{dt} = \alpha\Lambda(t)SV(t) - (\delta_{SV1} + \beta_{SV1})SVI_1(t)$$

$$\frac{dSVR_1(t)}{dt} = \beta_{SV1}SVI_1(t) - \alpha\Lambda(t)SVR_1(t)$$

$$\frac{dR_1V(t)}{dt} = (1-f)\nu_R(t)R_1(t) - \alpha\Lambda(t)R_1V(t)$$

Secondary Infection

$$\frac{dI_2(t)}{dt} = \alpha\Lambda(t)R_1(t) - (\delta_2 + \beta_2)I_2(t)$$

$$\frac{dR_2(t)}{dt} = \beta_2 I_2(t) - \nu_R(t)R_2(t)$$

$$\frac{dSVI_2(t)}{dt} = \alpha\Lambda(t)SVR_1(t) - (\delta_{SV2} + \beta_{SV2})SVI_2(t)$$

$$\frac{dSVR_2(t)}{dt} = \beta_{SV2}SVI_2(t)$$

$$\frac{dR_1VI_2(t)}{dt} = \alpha\Lambda(t)R_1V(t) - (\delta_{RV2} + \beta_{RV2})R_1VI_2(t)$$

$$\frac{dR_1VR_2(t)}{dt} = \beta_{RV2}R_1VI_2(t)$$

The compartments of the model are given in **Table 2** and illustrated in **Figure 1**.

2.3 Parameters of the Model

The parameters of the model are chosen to align with the dengue epidemic data in the Philippines in 2016, 2017, 2018 during the time period of vaccination (April 1, 2016 to December 1, 2017) and the time period of reported deaths of vaccinated children (April 1, 2016 to September 30, 2018). The time dependent infection rate $\alpha \Lambda(t)$ is specific to a population of 875,000 5–14 years olds, since infection rates are age-specific. The total weekly reported cases for all ages is given in **Supplementary Figure S8** for 2016, **Supplementary Figure S9** for 2017, **Supplementary Figure S10** for 2018 [8]. $\Lambda(t)$ is a cubic spline approximation of this total weekly reported cases for all ages, with a separate scaling factor for each of the years 2016, 2017, 2018, as in **Table 1**:

$$scaling\ factor = \begin{cases} 0.0031 \times 875,000, & 1 \le t < 52, \quad (2016), \\ 0.0022 \times 875,000, & 52 \le t < 104, \quad (2017), \\ 0.0030 \times 875,000, & 104 \le t < 156, \quad (2018). \end{cases}$$
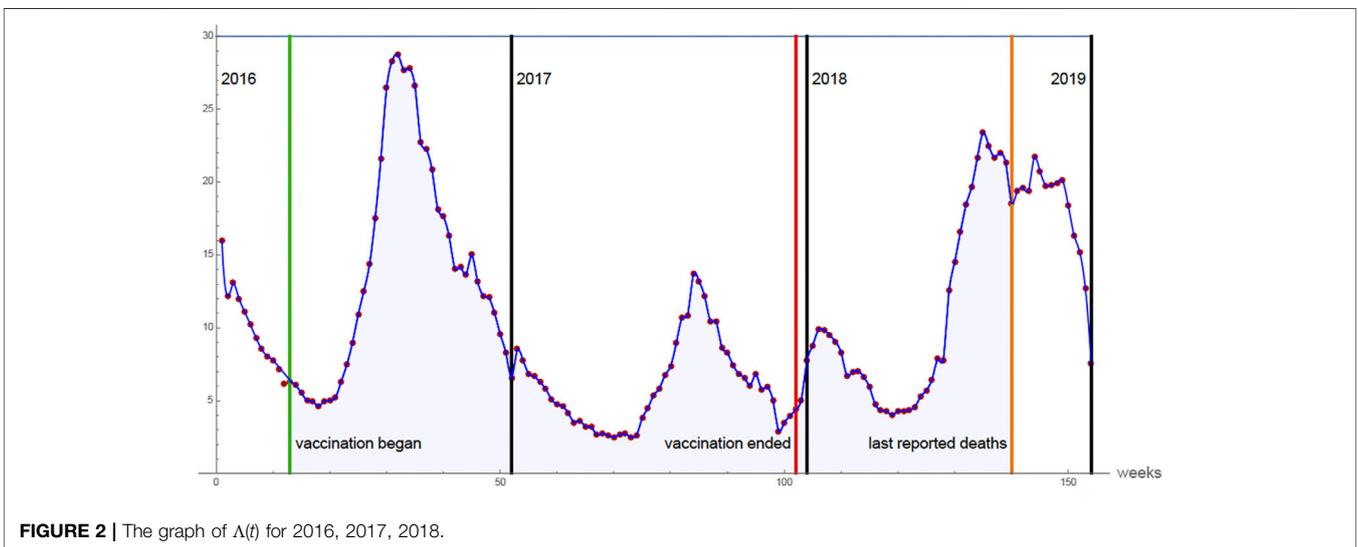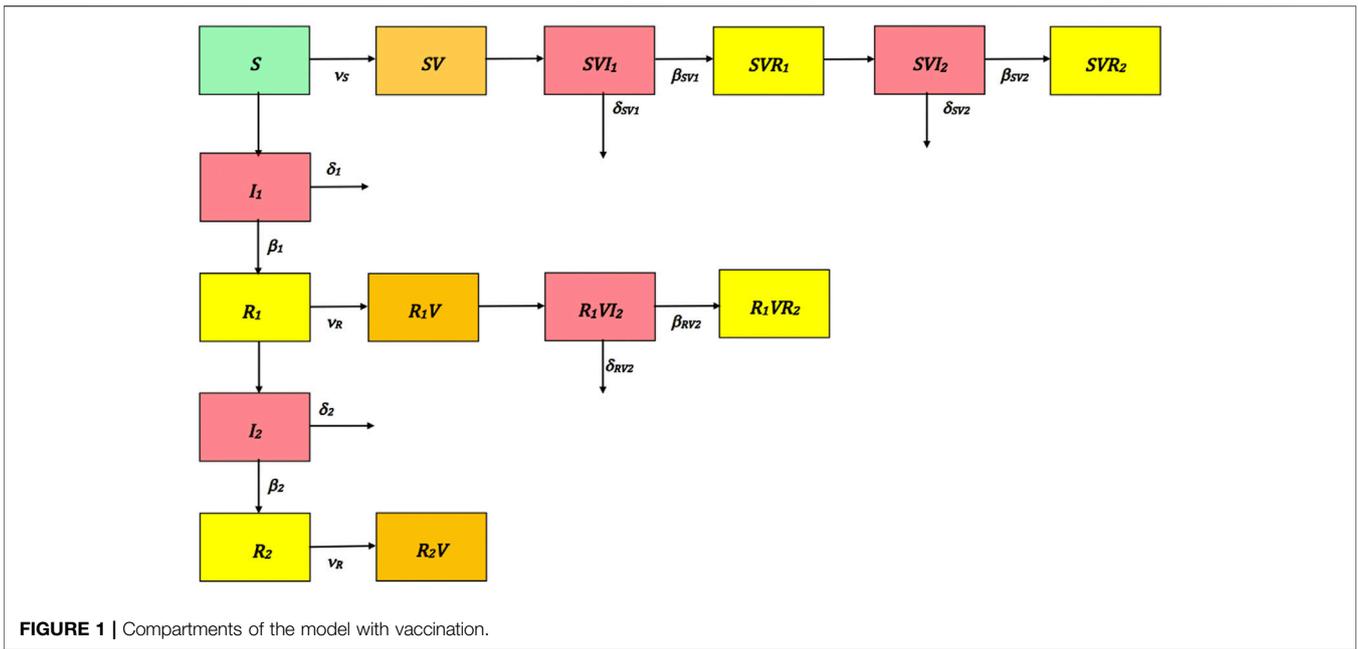
The graph of $\Lambda(t)$ is given in **Figure 2**.

$\Lambda(t)$ indirectly models the infection rate of these children due to mosquitoes. The seasonality of the mosquito population is incorporated indirectly into $\Lambda(t)$. We do not model the mosquito population directly, but assume the mosquito infection rate of 5–14 years olds is proportional to the reported case data in this age range. The value of α is chosen so that the dynamics of the model equations yield the general epidemic data for ages 9, 10, 11, in 2016, 2017, 2018, respectively, and for the 19 reported deaths of vaccinated 875,000 9 years olds for whom the vaccination failed in the period April 2016 to September 2018.

The time dependent vaccination rate $\nu_S(t)$ of previously uninfected 9 years olds incorporates multiple doses. This parameter involves a rate per week corresponding to the vaccine-effectiveness. We first assume a weekly rate 0.06, which corresponds to 70% effectiveness overall (**Figure 4**). The vaccine-effectiveness percentage is controversial, and we will explore outcomes with other values [11–13]. We assume the time dependent vaccination rate $\nu_R(t)$ of previously infected susceptibles is the same as $\nu_S(t)$, and the fraction of vaccination effectiveness is also the same. The formula for $\nu_S(t)$ is

$$\nu_S(t) = \begin{cases} 0.0, & 0 \le t < 13; \\ 0.06, & 13 \le t \le 102; \\ 0.0, & 102 < t. \end{cases} \quad (1)$$

The time independent parameters of the model are given in **Table 3**. The recovery rates per week of infected individuals are $\beta_1, \beta_2, \beta_{SV1}, \beta_{SV2}, \beta_{RV2}$, all equal to one, which means that the average period of symptomatic infection is approximately 1 week. The death rates per week of infected individuals are $\delta_1, \delta_2, \delta_{SV1}, \delta_{SV2}, \delta_{RV2}$. It is assumed that deaths occur only during the periods of symptomatic infection. We assume that the death rate of unvaccinated secondary infection (δ_2) is 10 times the death rate of unvaccinated primary infection (δ_1). We assume that the death rate (δ_{SV1}) of vaccinated not previously infected, who

FIGURE 1 | Compartments of the model with vaccination.

FIGURE 2 | The graph of $\Lambda(t)$ for 2016, 2017, 2018.

become infected, is approximately 7 times the death rate (δ_1) of unvaccinated primary infected [14]. The values of the parameters are determined by these assumptions and the fit of model solutions to reported data.

## 2.4 Previously Infected in the 875,000 Vaccinated 9 year Olds

The number of previously infected in the population of 875,000 vaccinated 9 years olds is calculated according to the reported cases in the years 2008–2017. In any 2-years age bracket for these years there are $\approx$ 4,600,000 children in the Philippines [9]. For 2013, there were 186,000 reported cases in all ages and 72,000 cases ages 1 to 10 (**Supplementary Figure S11**). Thus, the

TABLE 3 | Parameters of the model.

Symbol	Value	Meaning
α	8.5×10^{-7}	Infection rate parameter
f	0.7	Vaccinated fraction with vaccine effective
β_1	1.0	I_1 recovery rate parameter
β_2	1.0	I_2 recovery rate parameter
β_{SV1}	1.0	$SV1$ recovery rate parameter
β_{SV2}	1.0	$SV2$ recovery rate parameter
β_{RV2}	1.0	$RV2$ recovery rate parameter
δ_1	0.0031	I_1 death rate parameter
δ_2	0.031	I_2 death rate parameter
δ_{SV1}	0.02	SVI death rate parameter
δ_{SV2}	0.002	$SV2$ death rate parameter
δ_{RV2}	0.001	$RV2$ death rate parameter

TABLE 4 | The reported number of infected in the population of vaccinated children, 2013–2017.

Year	Reported cases all ages	Reported cases in data age bracket	Reported cases in age bracket
2013	= 186,416	Ages 1–10 ≈ 72,000 (**Supplementary Figure S4**)	Ages {5, 6} $\frac{875,000}{4,600,000} \times 72,000 \times .2 \approx 2,739$
2014	= 113,485	Ages 5–14 ≈ 45,000 (**Supplementary Figure S12**)	Ages {6, 7} $\frac{875,000}{4,600,000} \times 45,000 \times .2 \approx 1,712$
2015	= 200,415	Ages 5–14 ≈ 77,000 (**Supplementary Figure S13**)	Ages {7, 8} $\frac{875,000}{4,600,000} \times 77,000 \times .2 \approx 2,929$
2016	= 220,518	Ages 5–9 (**Supplementary Figure S2**)	Ages {8, 9} $\frac{875,000}{4,600,000} \times 48,000 \times .4 \approx 3,652$
2017	= 131,837	Ages 5–14 ≈ 51,000 (**Supplementary Figure S4**)	Ages {9, 10} $\frac{875,000}{4,600,000} \times 51,000 \times .2 \approx 1,940$
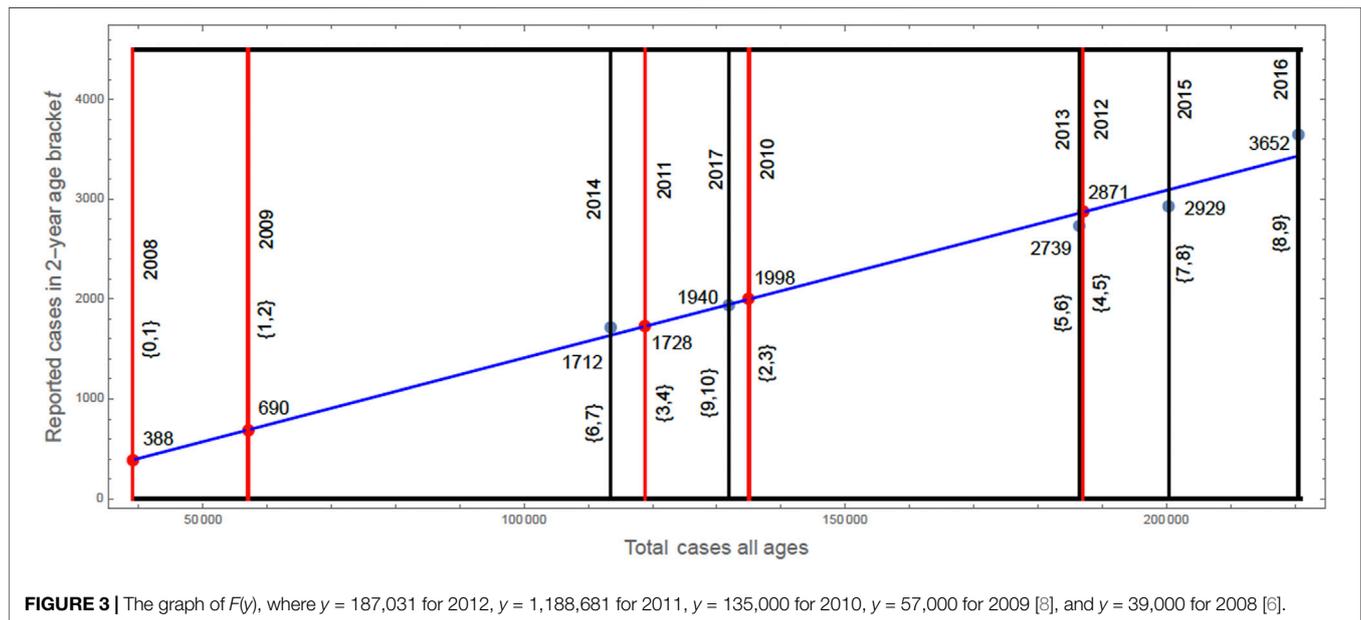
FIGURE 3 | The graph of $F(y)$, where $y = 187,031$ for 2012, $y = 1,188,681$ for 2011, $y = 135,000$ for 2010, $y = 57,000$ for 2009 [8], and $y = 39,000$ for 2008 [6].

number of reported cases in the age bracket {5, 6} in 2013 of vaccinated 9 years olds was $\frac{875,000}{4,600,000} \times 72,000 \times 0.2 \approx 2,700$ (the factor 0.2 accounts for the fraction in the age bracket {5, 6} in the age bracket {1,10}). Similar calculations for 2014, 2015, 2016, 2017 are given in **Table 4**.

In the years 2008–2012, the data in [8] is non-specific to age. We extrapolate the data in **Table 4** for these years by defining the function $F(y) = 0.0168\,y - 265.856$, as the least squares fit to the number of reported cases in the 2-years age brackets in **Table 4**, where y is the reported number for cases of all ages in the year of this age bracket. The graph of $F(y)$ is given in **Figure 3**.

The total number of reported previous infections for the population of 875,000 9 year olds is $388 + 690 + 1712 + 1728 + 1940 + 1998 + 2,739 + 2,871 + 2,929 + 3,652 \times 1/2 \approx 18,821$. This reported case data is adjusted to account for unreported cases. In [15] it is claimed that underreported cases are approximately 4.7 times the number of reported cases annually in the years 2010–2014 (we assume the number of reported deaths is accurate). We thus obtain $18,821 \times 4.7 \approx 88,500$ previously reported cases in the population of 875,000 9 years olds. We set $R_1(0) = 80,000$ and $R_2(0) = 8,500$ to account for the cumulative number of previously infected, primary and secondary, in the population of 875,000 8 and 9 years olds.

2.5 Initial conditions of the Model

The initial conditions of the model (**Table 5**) are chosen to correlate with the data of reported cases and reported deaths of the population of vaccinated 875,000 8 and 9 years olds in the time period April 3, 2016 to December 1, 2017 (beginning to ending of the vaccination program) and April 3, 2016 to September 30, 2018 (beginning to ending to the reported deaths in this population). The initial conditions for the compartments of the model are approximately 95% of 875,000, because it is assumed approximately 5% of the vaccinated children will not be successfully monitored for infection.

3 RESULTS

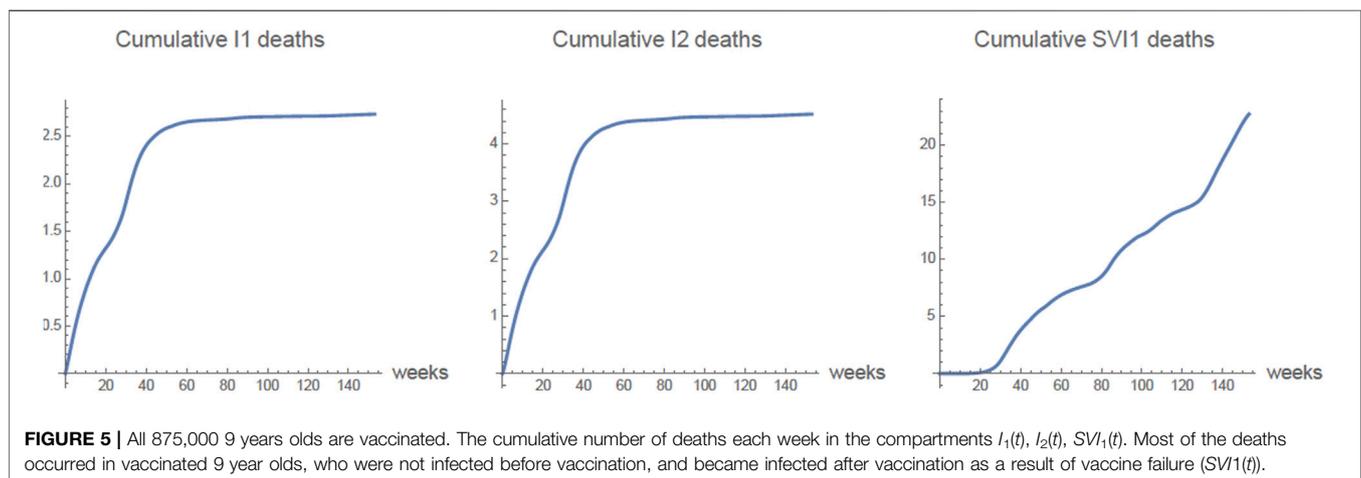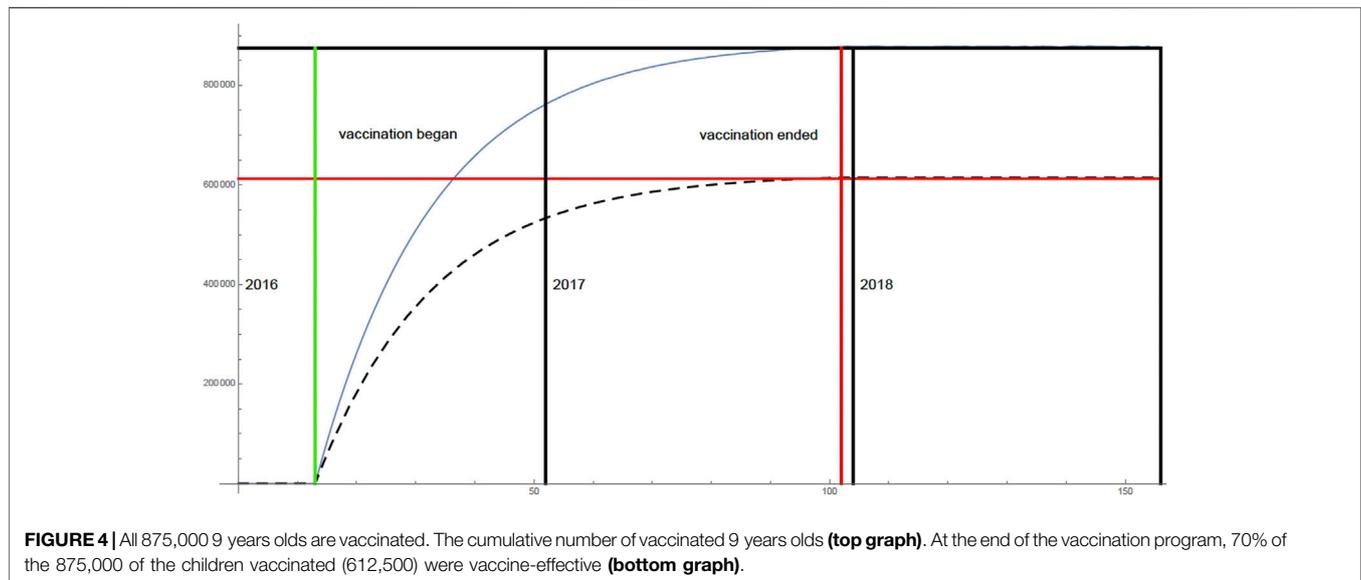### 3.1 All 875,000 9 year Olds are Vaccinated

The model output for the case that all 875,000 9 years olds are vaccinated is given below.

In **Figure 4** the graph of the cumulative number of vaccinated is given. The vaccine efficiency is 70%, which is interpreted as failure of the vaccine to prevent infection in 30% of the vaccinated 875,000 9 years olds.

In **Figure 5** the graphs of the cumulative number of deaths each week of the 875,000 vaccinated 9 years olds is given for
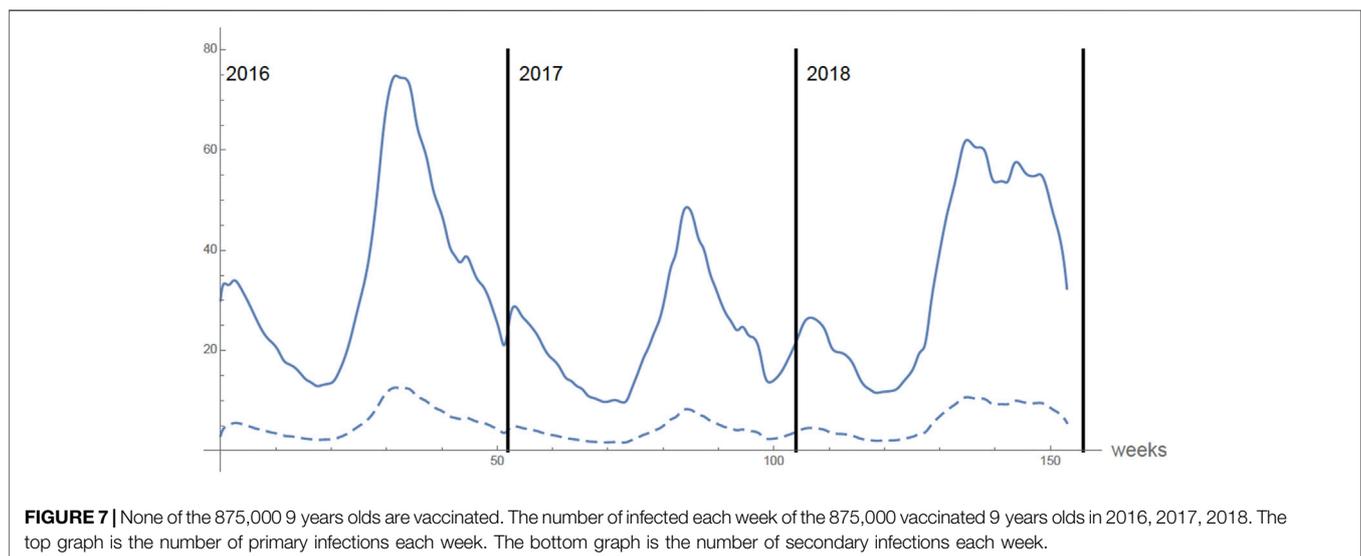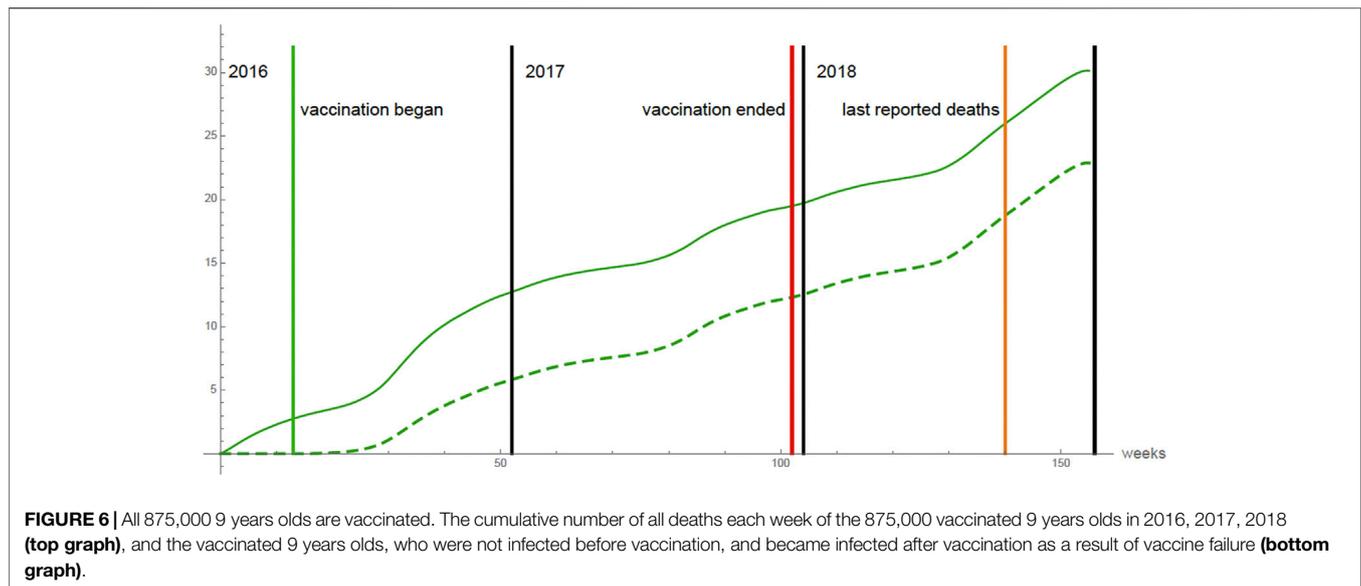
TABLE 5 | Initial conditions of the model. Time 0 corresponds to April 3, 2016.

Initial conditions	Value	Meaning
$S(0)$	700, 000	Not previously infected
$I_1(0)$	30	Primary infected
$I_2(0)$	3	Secondary infected
$R_1(0)$	120, 000	Recovered primary infected
$R_2(0)$	10, 000	Recovered secondary infected
$SV(0)$	0	Not previously infected, vaccinated
$SVI_1(0)$	0	Vaccinated, primary infected
$SVI_2(0)$	0	Vaccinated, secondary infected
$R1V(0)$	0	Primary infected, recovered, vaccinated
$R1VI_2(0)$	0	Primary infected, recovered, vaccinated, secondary infected
$R1VR_2(0)$	0	Primary infected, recovered, vaccinated, secondary infected, recovered

FIGURE 4 | All 875,000 9 years olds are vaccinated. The cumulative number of vaccinated 9 years olds **(top graph)**. At the end of the vaccination program, 70% of the 875,000 of the children vaccinated (612,500) were vaccine-effective **(bottom graph)**.

FIGURE 5 | All 875,000 9 years olds are vaccinated. The cumulative number of deaths each week in the compartments $I_1(t)$, $I_2(t)$, $SVI_1(t)$. Most of the deaths occurred in vaccinated 9 year olds, who were not infected before vaccination, and became infected after vaccination as a result of vaccine failure ($SVI_1(t)$).

the compartments $I_1(t)$, $I_2(t)$, $SVI_1(t)$. The cumulative number of deaths in the compartments $SVI2$ and $R1VI2$ are negligible.

In **Figure 6** the graph of the cumulative number of all deaths each week of the 875,000 vaccinated 9 years olds is given. The number of all deaths in 2016, 2017, 2018 is ≈30. From the

FIGURE 6 | All 875,000 9 years olds are vaccinated. The cumulative number of all deaths each week of the 875,000 vaccinated 9 years olds in 2016, 2017, 2018 **(top graph)**, and the vaccinated 9 years olds, who were not infected before vaccination, and became infected after vaccination as a result of vaccine failure **(bottom graph)**.

FIGURE 7 | None of the 875,000 9 years olds are vaccinated. The number of infected each week of the 875,000 vaccinated 9 years olds in 2016, 2017, 2018. The top graph is the number of primary infections each week. The bottom graph is the number of secondary infections each week.

beginning of the vaccination program (April 4, 2016) to the date of the last reported deaths (September 2018), 19 of the deaths occurred in vaccinated 9 years olds, who were not infected before vaccination, and became infected after vaccination as a result of vaccine failure, which agrees with the number reported by the Philippines Department of Public Health during this time period.
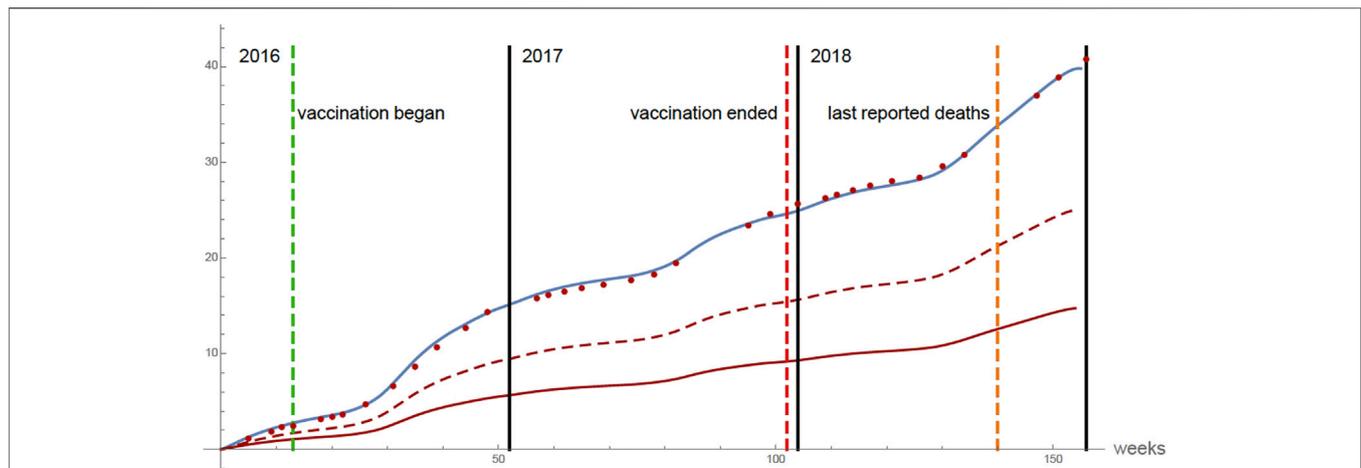
3.2 None of the 875,000 Nine Year Olds are Vaccinated

The model output for the case that none of the 875,000 9 years olds are vaccinated is given below. The only change in the parameters is that $v_S(t) \equiv 0$ and $v_R(t) \equiv 0$. In **Figure 7** the graph of the number of infected each week of the 875,000 (unvaccinated) 9 years olds is given. The number of secondary

infected each week of these 875,000 9 years olds is $\approx 3.6\%$ of the number of primary infected.

In **Figure 8** the graph of the total cumulative number of all deaths each week of the 875,000 (unvaccinated) 9 years olds is given. The number of all deaths between the beginning of the vaccination program (April 4, 2016) and the last reported deaths (September 2018) is ≈ 30. The number of all deaths in 2016, 2017, 2018 is ≈ 40.

3.3 Only Previously Infected of the 875,000 Nine Year Olds are Vaccinated

The model output for the case that only previously infected of the 875,000 9 years olds are vaccinated is given below. The change in the parameters is that $v_S(t) \equiv 0$ and $v_R(t) = 0.06$ for $13 \leq t \leq 102$ and $v_R(t) = 0$ otherwise.

FIGURE 8 | None of the 875,000 9 years olds are vaccinated. Top graph: cumulative total number of all deaths each week of the 875,000 (unvaccinated) 9 years olds. The red dots correspond to a scaling of the reported case data for total cases of all ages [8]. The scaling accounts for the total deaths of the 875,000 9 years olds in the population (the scaling factor is 0.014 as in **Figure 4**). Middle graph: cumulative total secondary infected deaths. Bottom graph: cumulative total primary infected deaths.
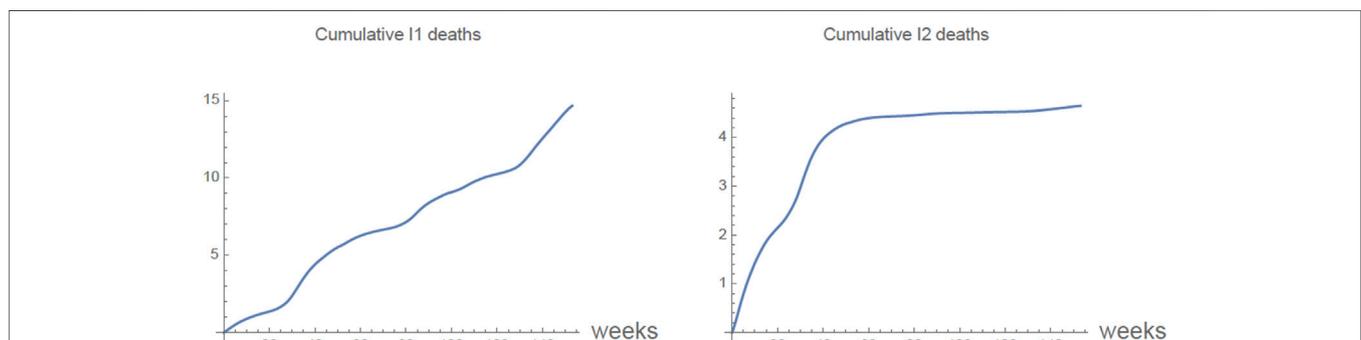
FIGURE 9 | Only previously infected of the 875,000 9 years olds are vaccinated. The cumulative number of deaths each week of primarily infected $I_1(t)$ and secondary infected $I_2(t)$.

In **Figure 9** the graphs of the cumulative number of deaths each week in the case that only previously infected are vaccinated are given for the primary infected cases $I_1(t)$ and secondary infected cases $I_2(t)$. The cumulative number of deaths in the compartments $SVI1$, $SVI2$ and $R1VI2$ are negligible.

In **Supplementary Figure S11** (Supplementary Materials) the graph of the total cumulative number of all deaths each week is given for the case that only previously infected are vaccinated. In this case the number of deaths between the beginning of the vaccination program April 4, 2016 and the last reported deaths September 2018 is ≈15. The number of all deaths in 2016, 2017, 2018 is ≈20.

3.4 Varying the Fraction of Vaccination Efficacy

In this section we vary the parameter f corresponding to the fraction of vaccinated for which the vaccine used in the

Philippines was effective. The value of f depends on strain serotypes 1–4, specific locations, age levels at vaccination, serostatus, and other factors. Currently, new vaccines are being developed and undergoing clinical trials with possible improved efficacy. The World Health Organization has reported various efficacies from Phase 3 clinical trials, ranging from 43% to 79% [11].

In the example above, for the case that only previously infected are vaccinated, the percentage vaccinated was 70% ($f = 0.7$). In **Supplementary Figure S12** (Supplementary Materials), for the case that only previously infected are vaccinated, the vaccine efficacy is 80% ($f = 0.8$). In **Supplementary Figure S13** (Supplementary Materials), for the case that only previously infected are vaccinated, the vaccine efficacy is 60% ($f = 0.6$).

In all three examples of the model output ($f = 0.6$, $f = 0.7$, $f = 0.8$), the cumulative number of deaths is less for the vaccinated 875,000 children than the cumulative number of deaths without

TABLE 6 | Values of reported cases and cumulative deaths of vaccinated 9 year old children.

	No vaccination	All vaccinated		
		60% Efficacy	70% Efficacy	80% Efficacy
Total reported cases in 2016, 2017, 2018	5, 533	2, 812	2,366	1,920
Total cumulative deaths in 2016, 2017, 2018	40	38	30	23
Total cumulative deaths April, 2016–September, 2018	30	30	23	17
Total cumulative deaths of vaccinated previously uninfected April, 2016–September, 2018	—	25	19	12
Only previously infected vaccinated				
	—	60% Efficacy	70% Efficacy	80% Efficacy
Total reported cases in in 2016, 2017, 2018	—	5, 149	5,082	5,015
Total cumulative deaths in 2016, 2017, 2018	—	20	20	19
Total cumulative deaths April, 2016–September, 2018	—	15	15	15
Total cumulative deaths of vaccinated previously uninfected April, 2016–September, 2018	—	0	0	0

any vaccination. The number of cumulative deaths in the case that only previously infected children are vaccinated is approximately the same in all three examples. The number of cumulative deaths in the case that all children are vaccinated decreases proportionately as f increases. In **Table 6**, a comparison of model output for these cases is given. The unreported cases are assumed ≈ 5 times the number of reported cases, as in [15].

4 DISCUSSION

The dengue vaccination program in the Philippines, which began in April 2016, was halted in December, 2017, because of the number of deaths of vaccinated children that had occurred. A controversy surrounds this vaccination program, which has been claimed to be a disaster for the 875,000 9 years old children who were vaccinated [14]. The core issue in this controversy is the increased risk of severe dengue symptoms and deaths of vaccinated individuals who were previously uninfected. For dengue, a secondary infection, with a strain different from the primary infection, has greater symptoms severity [16]. It is claimed that vaccination for dengue mimics a primary infection, and a subsequent primary infection if the vaccine fails, acts like a secondary infection.

In 2018, WHO advised that prior screening for dengue infection was preferable, but if not feasible, general dengue vaccination programs could be administered to individuals age nine and older, if the population had a dengue endemicity rate higher than 80% [14]. In June 2021, the CDC Advisory Committee on Immunization Practices (ACIP) recommended use of Dengvaxia to prevent dengue in children aged 9–16 years, with laboratory-confirmed previous dengue virus infection and living in areas where dengue is common [17].

We have developed a model of the dengue vaccination program in the Philippines to provide understanding of the controversy surrounding this vaccination program. We used reported case data and reported mortality data from the Philippines Department of Health, to analyze quantitatively this vaccination program. We then reformulated our model to

correspond to the case that no vaccination program had occurred or only previously infected children had been vaccinated. Our results our summarized in **Table 4**. We varied the vaccine efficacy rate as 60, 70, and 80%. For all three efficacy rates, the number of deaths was as high or higher without the vaccination of all 875,000 children. For all three efficacy rates, the number of deaths was also higher with the vaccination of only previously infected in the population of 875,000 children.

The vaccination program in the Philippines may have prevented a significant number of deaths, although a controversy still surrounds the issue of whether the vaccine itself contributed to some of the deaths of the children uninfected before vaccination. If these children had not been vaccinated, it is likely that they would not have died. The fundamental axiom of medicine is to do no harm. If the vaccine fails to prevent a subsequent infection resulting in death in someone who has not been previously infected, the vaccine has caused harm. But what is the threshold of harm, as opposed to the society benefit of the vaccine for prevention of deaths?

This issue relates to the current general controversy surrounding vaccination programs, and their distrust by some within our societies. The issue of vaccine hesitancy is of major concern in public health policies throughout the world [18–20]. Negative publicity concerning vaccination programs relating to severe illness and mortality in vaccinated individuals contributes to vaccine hesitancy. In the current COVID-19 pandemic, vaccine hesitancy is a major concern for advancing vaccination levels to sufficiently high percentages in order to control the epidemics throughout the world [21,22,27].

In general, if the vaccine efficacy is sufficiently high, then a consequent significant reduction in the number of deaths justifies the vaccination program in all age groups. A further consideration is the possibility of reducing the number of cases that occur in a dengue epidemic by vaccinating most or all individuals in all age groups in an on-going general vaccination program. The model analysis reveals that the total number of dengue cases are greatly reduced if all individuals are vaccinated, but not significantly reduced if only previously infected

individuals are vaccinated. Thus, a general on-going vaccination program of all individuals could reduce the infected mosquito population, which would reduce the disease infection rate proportionately. Over time the dengue epidemic could be effectively eradicated.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: https://doh.gov.ph/statistics.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fams.2021.760259/full#supplementary-material

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