FOURTEENTH INTERNATIONAL

ROTAVIRUS SYMPOSIUM

MARCH 14–16 **2023** BALI INDONESIA

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Rotavirus Epidemiology and the Potential Impact of Vaccination in Dhaka, Bangladesh

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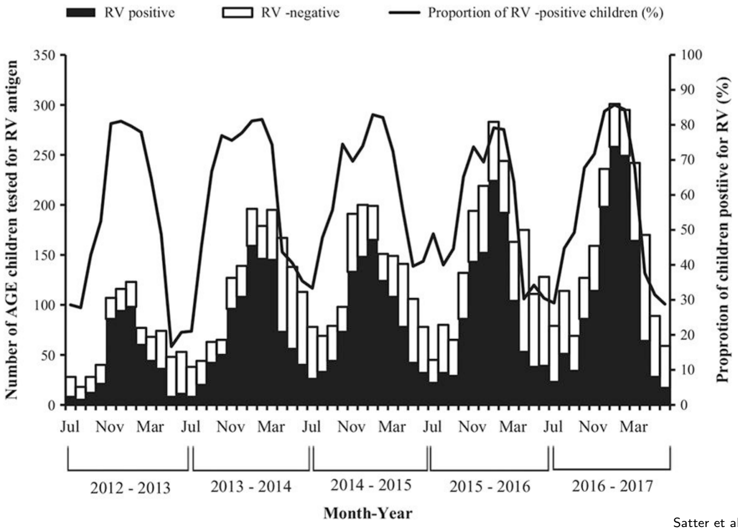
Rotavirus burden in Bangladesh from 8 sentinel sites



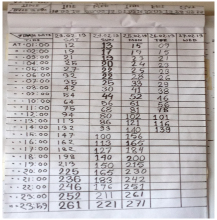
Satter et al. 2018

Rotavirus was detected in 64% (4832/7562) of children <5 years of age admitted with AGE

57% of patients with rotavirus infection were aged <12 months of age

Peak detection rates of >80% between November and February

Disparity in the levels of urbanization within Dhaka may influence spatial variation in rotavirus



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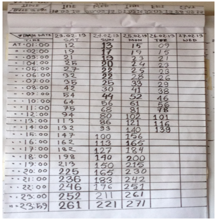
AT 01:00	12	13	15	09	
02:00	19	17	19	15	
03:00	21	19	23	21	
04:00	25	20	24	23	
05:00	27	22	25	23	
06:00	32	22	28	26	
07:00	35	25	33	29	
08:00	42	30	41	38	
09:00	54	44	52	46	
10:00	64	56	61	56	
11:00	75	68	81	78	
12:00	94	80	102	101	
13:00	113	86	121	116	
14:00	132	93	140	139	
15:00	147	100	156		
16:00	162	113	165		
17:00	182	127	184		
18:00	198	140	200		
19:00	213	150	215		
20:00	225	165	230		
21:00	236	183	242		
22:00	246	196	251		
23:00	252	211	261		
23:59	261	221	271		

The data comes from systematic stool samples of diarrheal patients presenting to **iccdr,b hospital in Dhaka**:

Every 25th (4%) patient sampled between 1990 and 1995 and 50th (2%) afterwards

Disparity in the levels of urbanization within Dhaka may influence spatial variation in rotavirus



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08:00	42	30	41	38	
09:00	54	44	52	46	
10:00	64	56	61	56	
11:00	75	68	81	78	
12:00	94	80	102	101	
13:00	113	86	121	116	
14:00	132	93	140	139	
15:00	147	100	156		
16:00	162	113	165		
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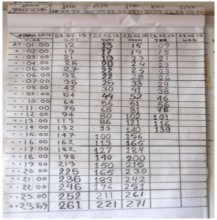
To use mathematical modeling to:

quantify the potential impact of rotavirus vaccines in Dhaka

Our Goal

Disparity in the levels of urbanization within Dhaka may influence spatial variation in rotavirus



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To use mathematical modeling to:

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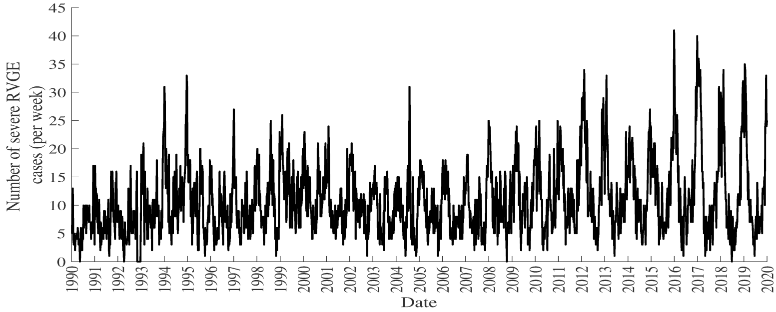
identify the optimal dosing schedule that would maximize vaccine benefits in Dhaka

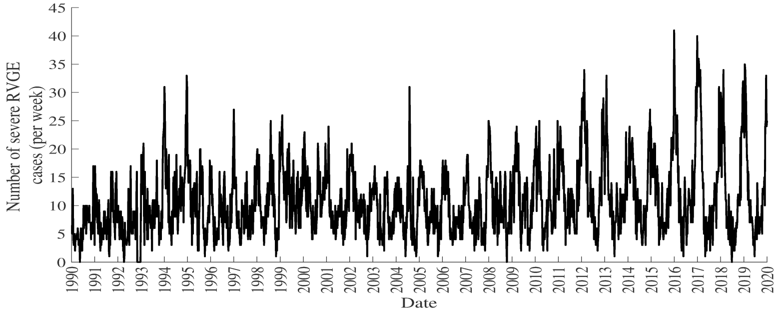


Year-round transmission with seasonal peaks

Confirmed cases per week can be more than 40

Annual average of more than 500 confirmed cases

Data overview - weekly cases and age distribution



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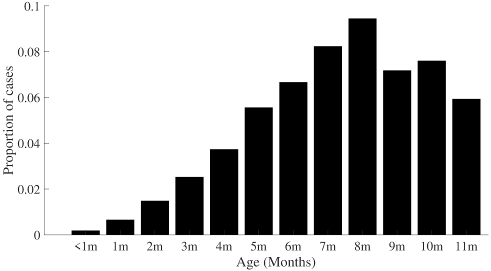
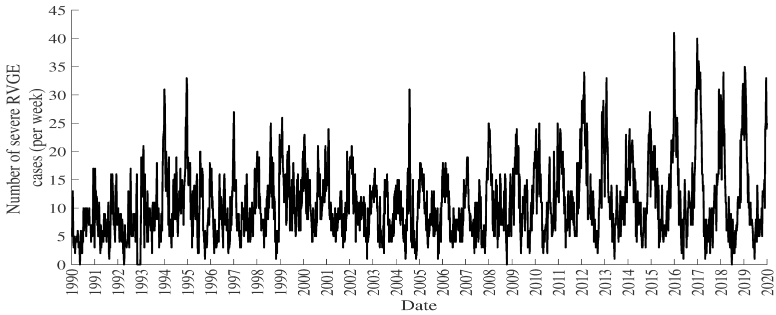


51% of the cases in infants aged 5-11 months

3% of cases in infants <3 months



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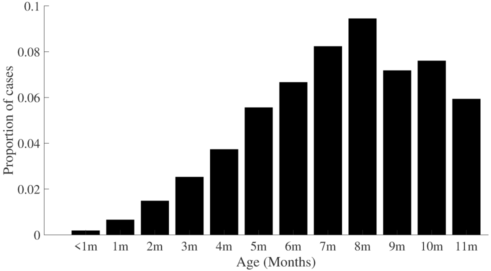
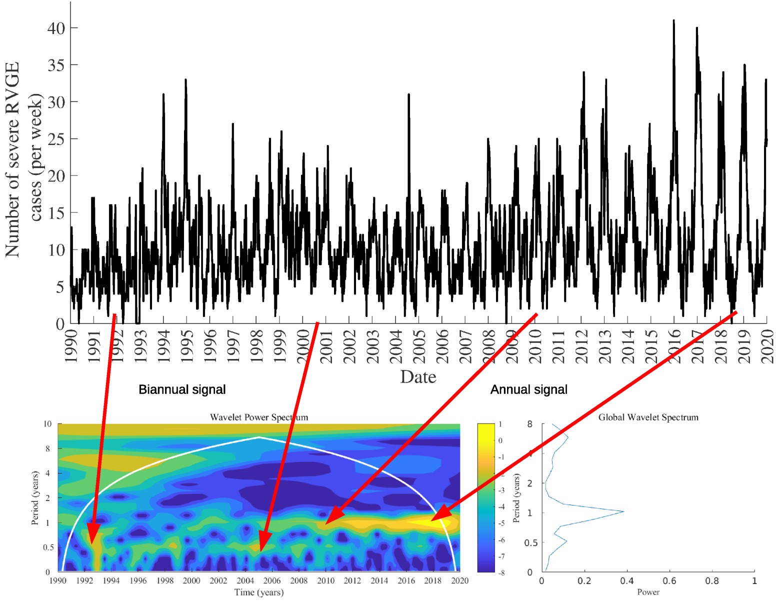


51% of the cases in infants aged 5-11 months

3% of cases in infants <3 months

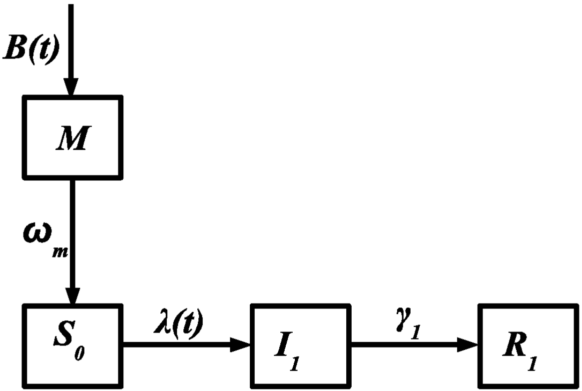
60% of cases in <1Y age group

28% of cases in 1Y age group



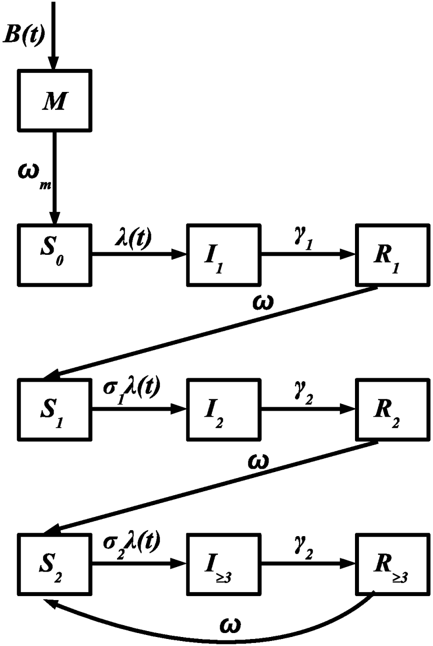
The intensity of the biannual signal is decreasing over time

The intensity of the annual signal is increasing over time



M – Maternal
S – Susceptible
I – Infective
R - Recovered

Model Description



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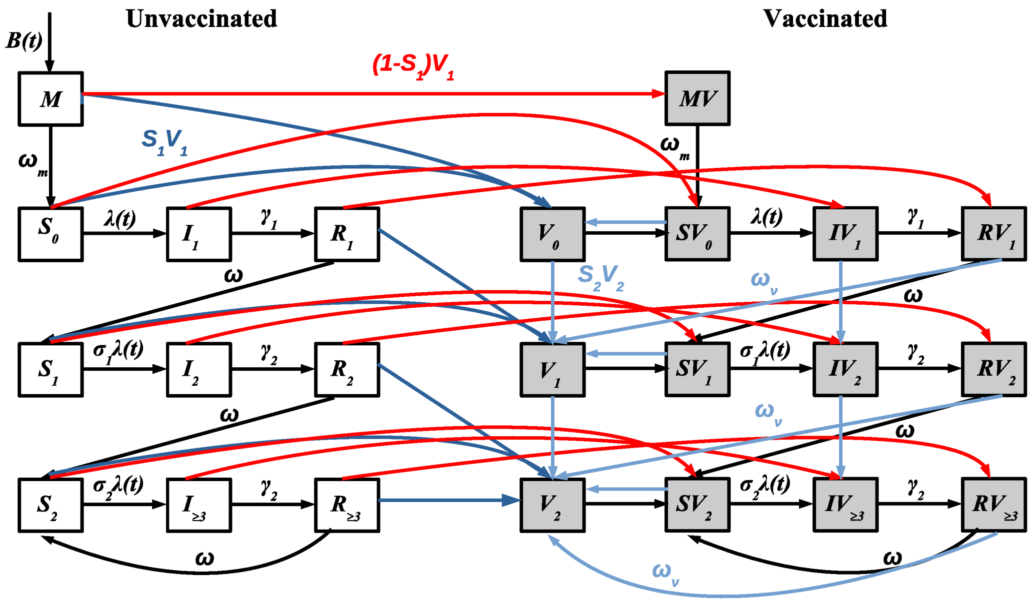
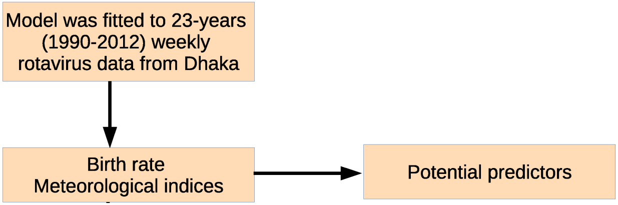
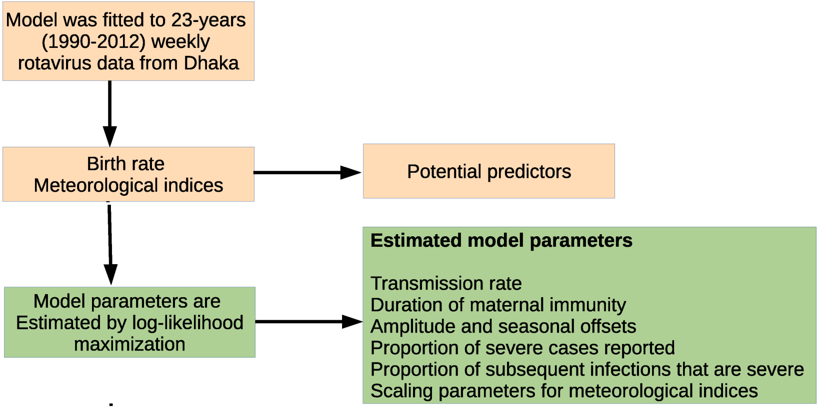

Unvaccinated
Vaccinated
B(t)
M
MV
(1-S1)V1
S1V1
ωm
ωm
S0
λ(t)
I1
γ1
R1
V0
SV0
λ(t)
IV1
γ1
RV1
ω
S2V2
ωv
ω
S1
σ1λ(t)
I2
γ2
R2
V1
SV1
σ1λ(t)
IV2
γ2
RV2
ω
ωv
ω
S2
σ2λ(t)
I≥3
γ2
R≥3
V2
SV2
σ2λ(t)
IV≥3
γ2
RV≥3
ω
ωv
ω

Model fitting procedure



Model fitting procedure



Model fitting procedure

Model was fitted to 23-years (1990-2012) weekly rotavirus data from Dhaka

Birth rate
Meteorological indices

Potential predictors

Model parameters are Estimated by log-likelihood maximization

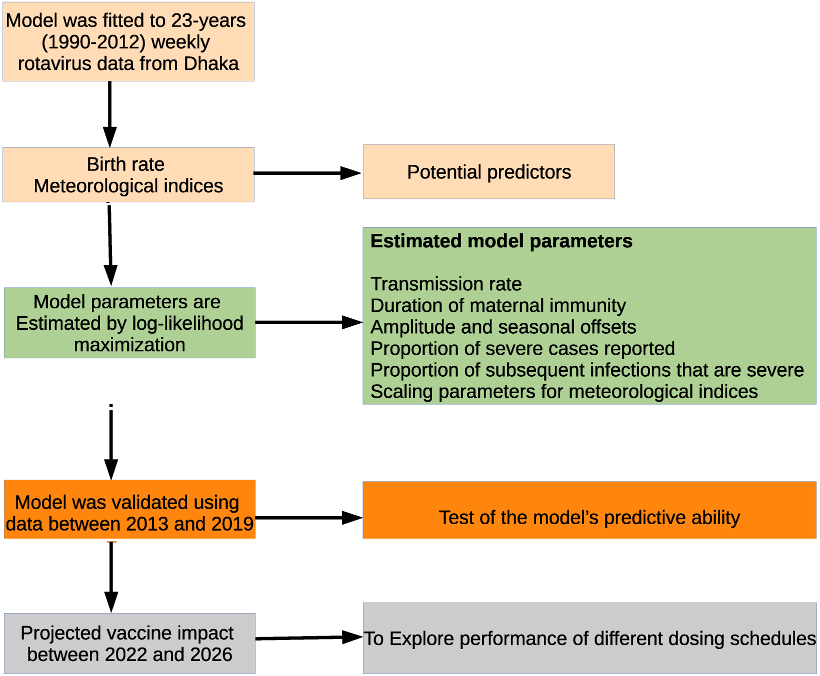
Estimated model parameters

Transmission rate
Duration of maternal immunity
Amplitude and seasonal offsets
Proportion of severe cases reported
Proportion of subsequent infections that are severe
Scaling parameters for meteorological indices

Model was validated using data between 2013 and 2019

Test of the model's predictive ability

Model fitting procedure



Dosing schedules

Schedule(weeks)	No. of doses	Age for vaccine (months)
6/10	2	2, 3
10/14	2	3, 4
6/10/14	3	2, 3, 4
6/10/40	3	2, 3, 9
1/6/10	3	0, 2, 3
1/10/14	3	0, 3, 4

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Model parameters describing vaccine effectiveness

- Vaccine response rate (S_C) $\rightarrow$ 50 - 90%

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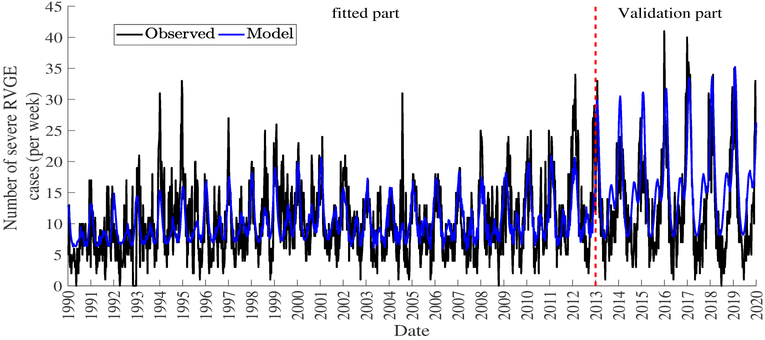
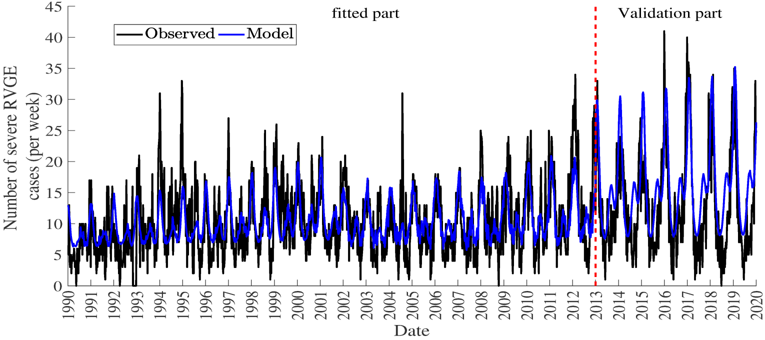
Model parameters describing vaccine effectiveness

- Vaccine response rate (S_C) $\rightarrow$ 50 - 90%
- Vaccine induced immunity duration (ω_v) $\rightarrow$ 3 - 60 months
- Vaccination coverage $\rightarrow$ fixed at 90%



Model was able to predict peak timing, duration and intensity of winter epidemics

Model was able to reproduce the shift from biannual to annual epidemics



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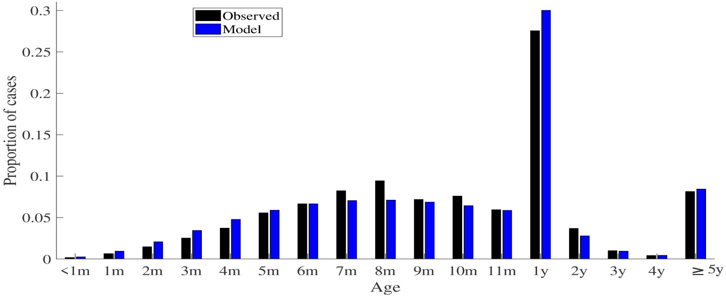
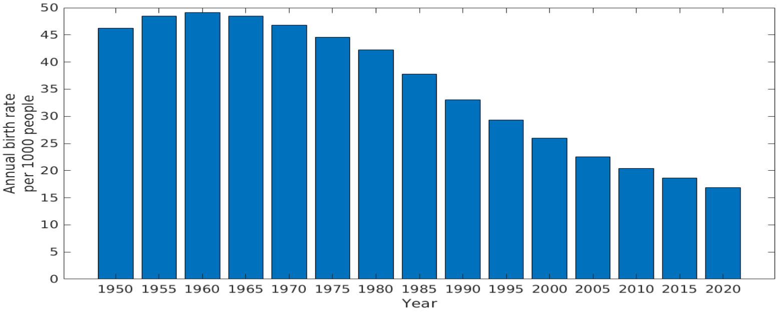


Model reasonably predicted the observed trend in age distribution

Good agreement with the proportion of cases in all age groups above 1 year

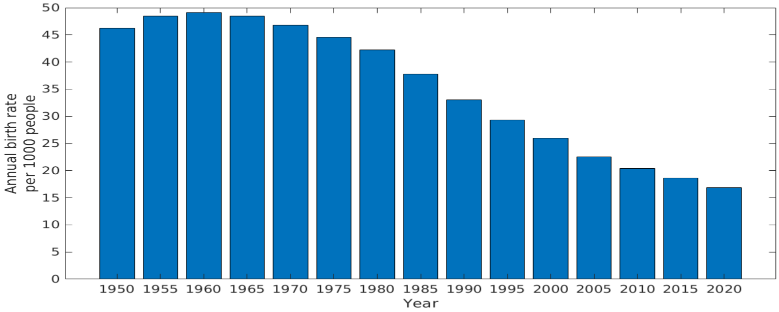
Over- or under-estimated proportion in some age group

Asare et al., 2022 (doi:10.1098/rspb.2021.2727)



Consistent declining in birth rate

A drop from 35 in 1990 to 18 in 2020



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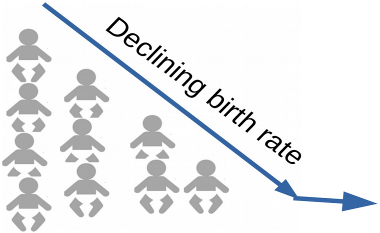
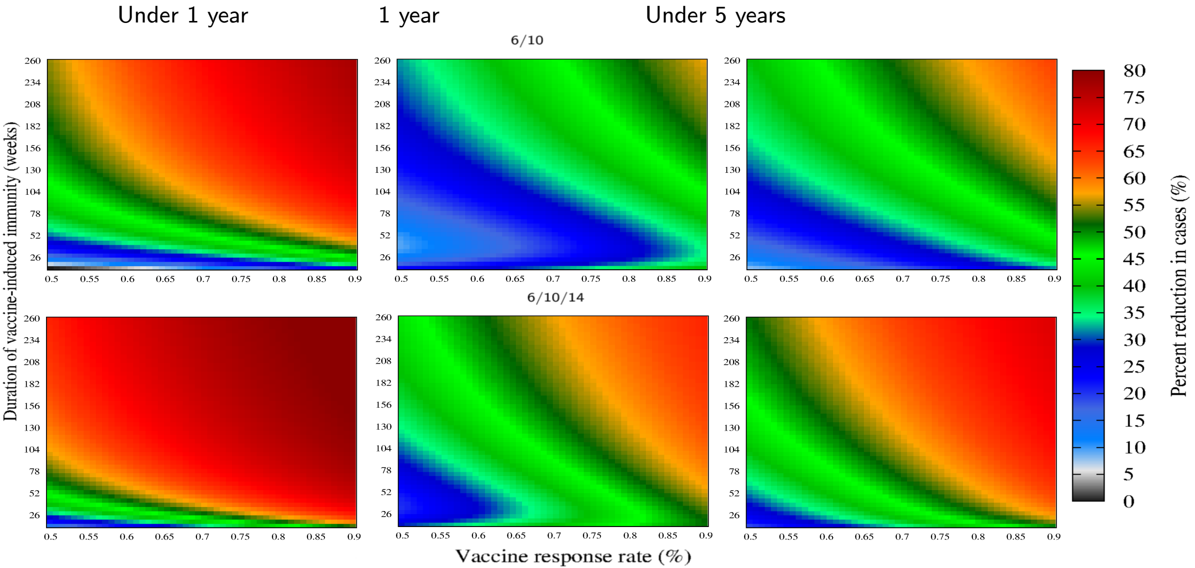


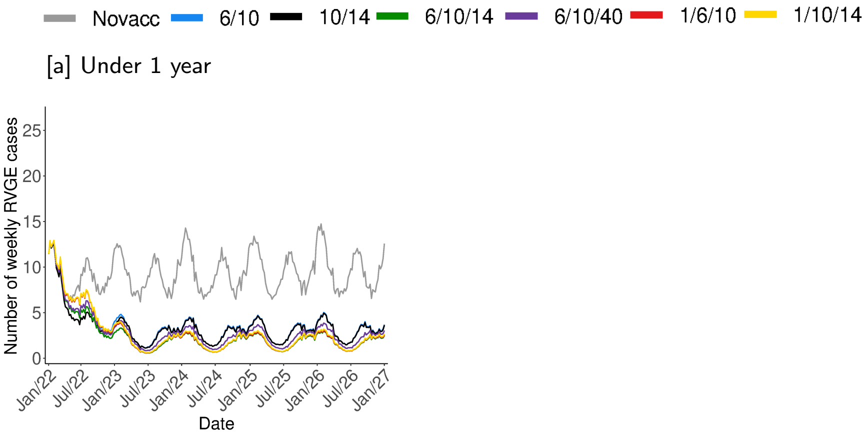
Reduction in susceptible → Rotavirus becoming seasonal

Results - projected vaccine impact: S_C and ω_v effect



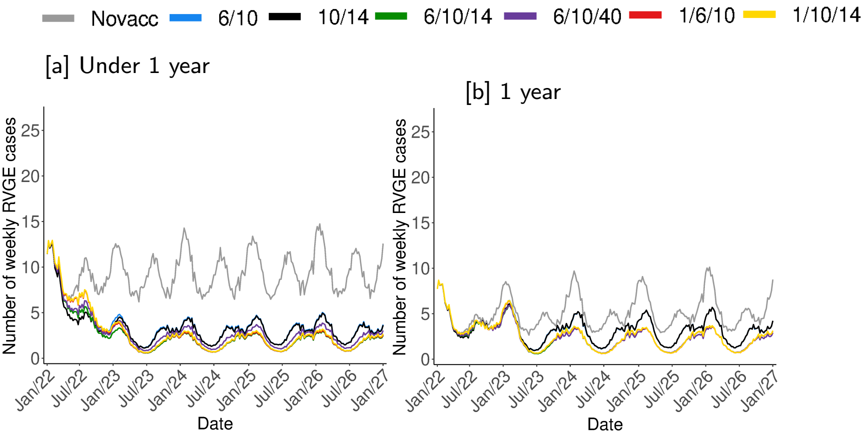
Vaccine response rate and duration of vaccine-induced immunity are important factors influencing vaccine performance

Results - Projected vaccine impact



Clear indication of vaccine induced protection

Results - Projected vaccine impact



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Lower vaccine protection

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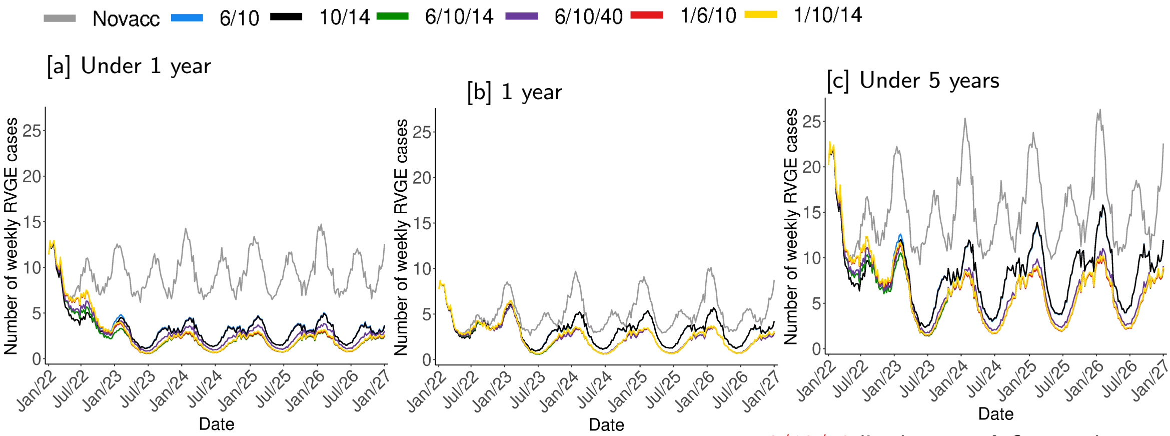


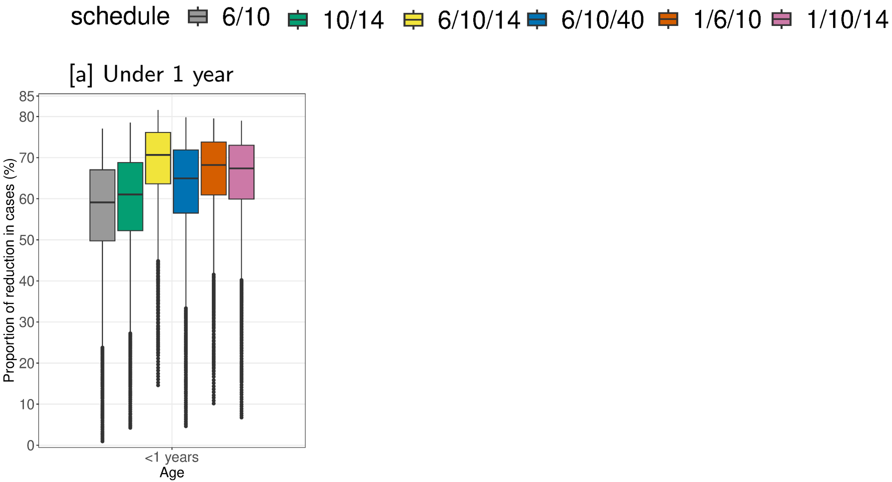
Clear indication of vaccine induced protection

Lower vaccine protection

6/10/40 lies between **infant** and **neonatal** schedules

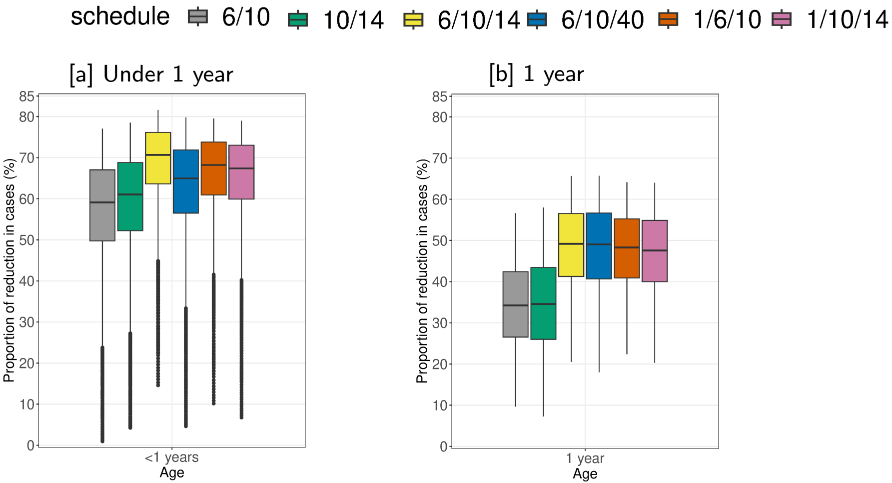
Moderate to substantial variations in vaccine impact among different dosing schedules

Differences exist among dosing schedules with the same number of doses



Median reductions range from
59% to 71%

Results - overall reductions over 5-year period



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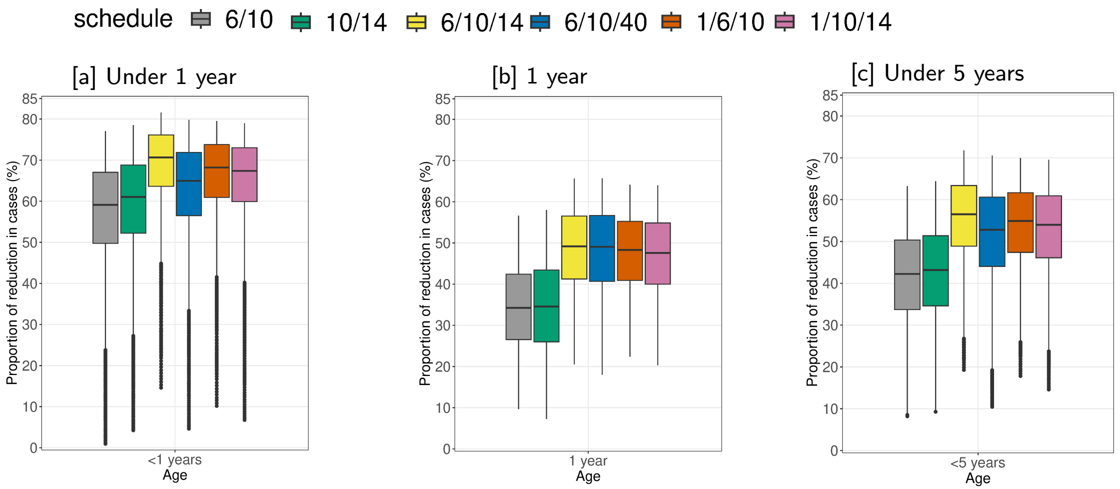

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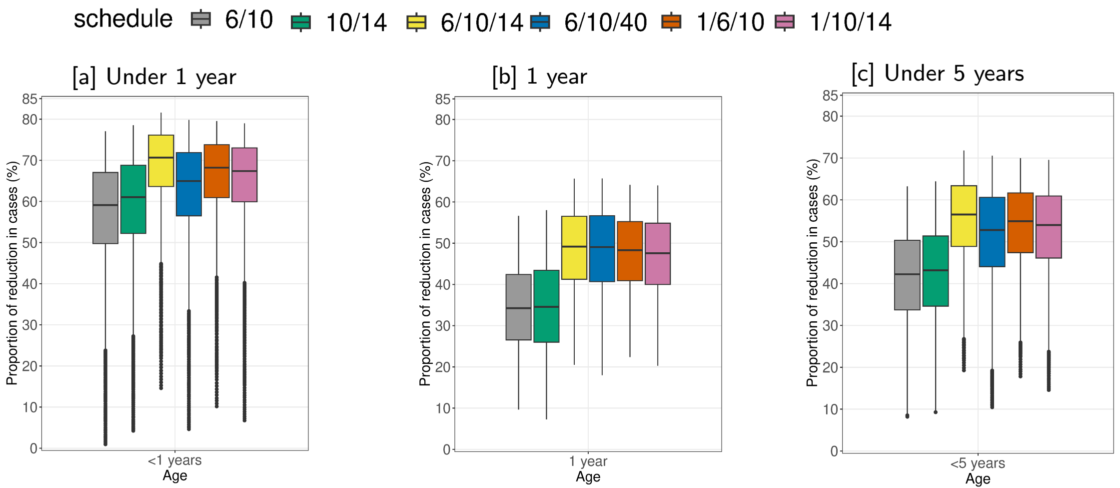

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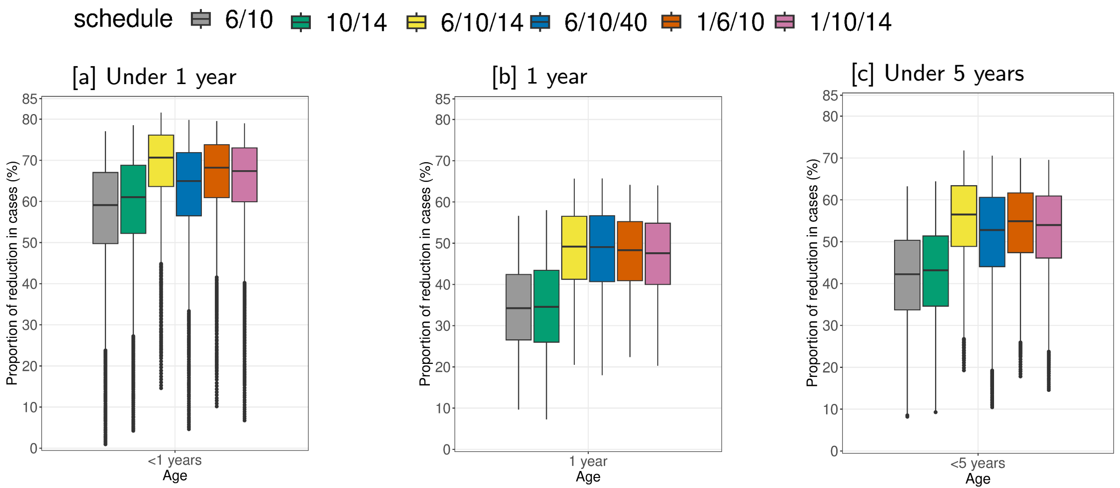

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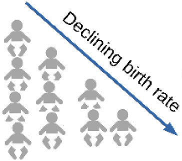
1/6/10 and **6/10/14** are the optimal dosing schedules

6/10 and **10/14** results in lower reduction in rotavirus incidence

Conclusions



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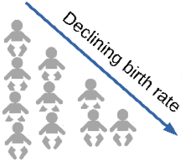
→ Declining in Rotavirus cases → Public Health benefits

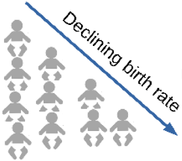
Conclusions



Declining in Rotavirus cases

Public Health benefits

The **6/10/14 and 1/6/10** provided the best and comparable reductions in cases



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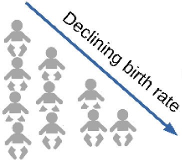

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Future cost-effectiveness analysis among these schedules could help identify the optimal schedule for Dhaka

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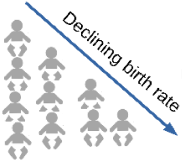

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Future cost-effectiveness analysis among these schedules could help identify the optimal schedule for Dhaka

The model can be useful to support policy-makers considering rotavirus vaccine introduction or switching to a different vaccine

ACKNOWLEDGMENTS

We thank our collaborators Monira Sarmin, A. S. G. Faruque and Tahmeed Ahmed at the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B)

This study is supported by NIH grant (NIH/NIAID R01AI112970) to Virginia Pitzer

Thank you

Rainfall-related indices

1. Weekly Degree of Wetness (dow)

$$dow = \frac{(\#\ of\ \ wetdays\ in\ a\ week) \times (total\ rainfall\ in\ a\ week)}{7}$$

2. Simple water balance model (wpre) - predicts presence of surface water

Temperature-related indices

3. Diurnal Temperature Range (dtr)

$$dtr = T_{max} - T_{min}$$

The force of infection at time t is given by:

Model 0

$$\lambda(t) = \beta_o \left(1 + \underbrace{\boxed{b_1 cos \left(\frac{2\pi t - \phi_1}{52.18} \right)}}_{\text{annual}} + \underbrace{\boxed{b_2 cos \left(\frac{2\pi t - \phi_2}{26.09} \right)}}_{\text{biannual}} \right) \sum_{i=1}^{\geq 3} \rho_i I_i(t)$$

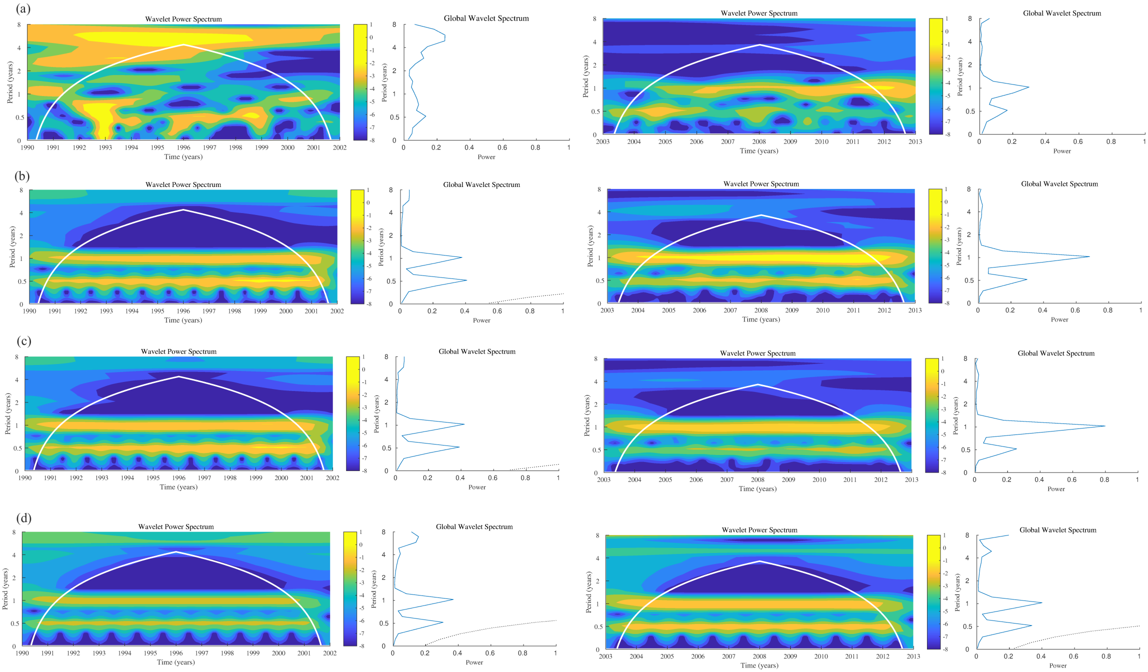
Model A

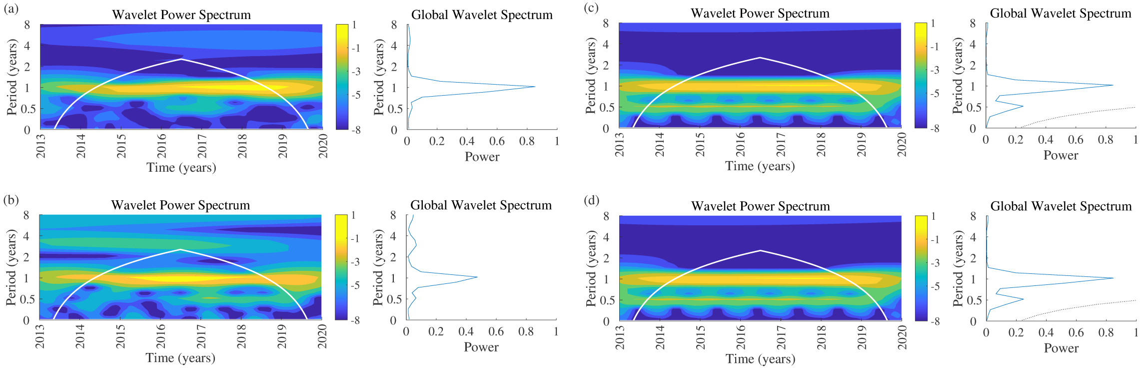
$$\lambda(t) = \beta_o \left(1 + \underbrace{\boxed{b_1 cos \left(\frac{2\pi t - \phi_1}{52.18} \right)}}_{\text{annual}} + \underbrace{\boxed{b_2 cos \left(\frac{2\pi t - \phi_2}{26.09} \right)}}_{\text{biannual}} + \underbrace{\boxed{\mathrm{dtr}_s(\mathrm{dtr})}}_{\text{Dtr}} + \underbrace{\boxed{\mathrm{dow}_s(\mathrm{dow})}}_{\text{Dow}} \right) \sum_{i=1}^{\geq 3} \rho_i I_i(t)$$

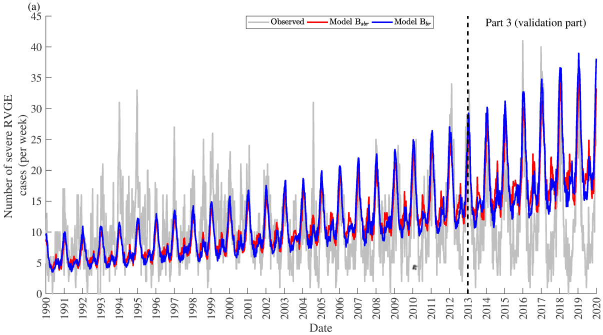
Model B

$$\lambda(t) = \beta_o \left(1 + \underbrace{\boxed{b_1 cos \left(\frac{2\pi t - \phi_1}{52.18} \right)}}_{\text{annual}} + \underbrace{\boxed{b_2 cos \left(\frac{2\pi t - \phi_2}{26.09} \right)}}_{\text{biannual}} + \underbrace{\boxed{\mathrm{dtr}_s(\mathrm{dtr})}}_{\text{Dtr}} + \underbrace{\boxed{\mathrm{wpre}_s(\mathrm{wpre})}}_{\text{Wpre}} \right) \sum_{i=1}^{\geq 3} \rho_i I_i(t)$$

Impact of birth rate and meteorological indices




(a)
Wavelet Power Spectrum
Global Wavelet Spectrum
Period (years)
Time (years)
Power
(b)
Wavelet Power Spectrum
Global Wavelet Spectrum
(c)
Wavelet Power Spectrum
Global Wavelet Spectrum
(d)
Wavelet Power Spectrum
Global Wavelet Spectrum


(a)
Observed
Model B_{sbr}
Model B_{br}
Part 3 (validation part)
Number of severe RVGE cases (per week)
Date
0
5
10
15
20
25
30
35
40
45
1990
1991
1992
1993
1994
1995
1996
1997
1998
1999
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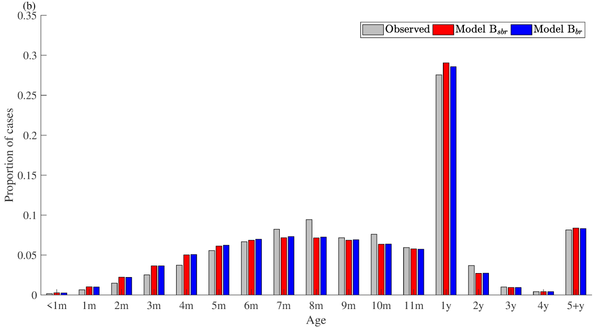
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018
2019
2020


(b)
Observed
Model B_{sbr}
Model B_{br}
Proportion of cases
Age
0
0.05
0.1
0.15
0.2
0.25
0.3
0.35
<1m
1m
2m
3m
4m
5m
6m
7m
8m
9m
10m
11m
1y
2y
3y
4y
5+y

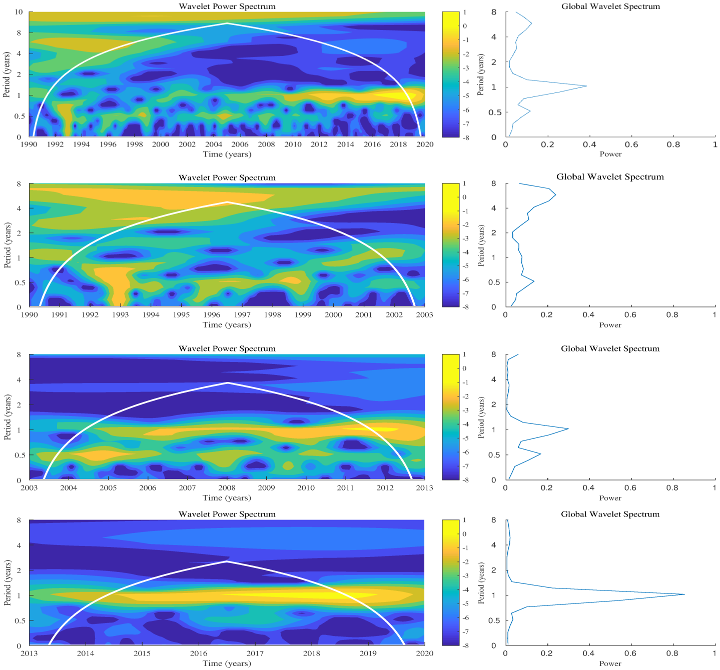
Model		Complete	Part 1	Part 2
Model 0	sbr	34110.640	18149.423	15748.394
	br	34158.287	18231.593	15701.277
Model A	sbr	34064.660	18137.479	15633.230
	br	34125.598	18218.051	15637.811
Model B	sbr	34036.499	18134.433	15630.233
	br	34113.684	18216.716	15636.716

sbr are models incorporating seasonal variation in the crude birth rate

br are models without seasonal variation in the crude birth rate

Based on AIC, the model with **Model B**$_{sbr}$ best fit the data

Data overview - observed shift from biannual to annual patterns - Dhaka



Complete (1990 - 2019)

Biannual at the beginning
Annual at the end

Part 1 (1990 - 2002)

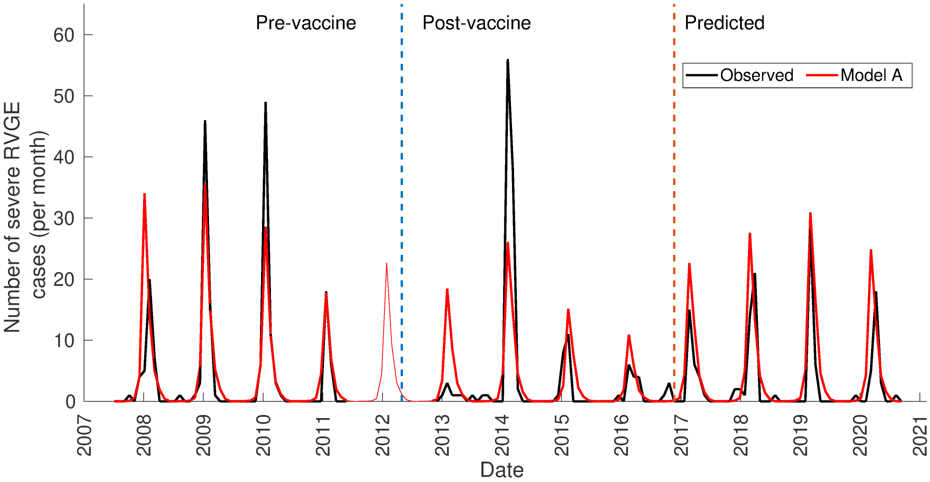
The intensity of the **biannual signal** is decreasing over time

Part 2 (2003 - 2012)

The intensity of the **annual signal** is increasing over time

Part 3 (2013 - 2019)

Rotavirus exhibits **strong annual cycle**



Satisfactory agreement between model and observed post-vaccination cases

Asare et al. 2020 (doi:10.1016/j.vaccine.2020.05.057)

$$\frac{\mathrm{dw_{pond}}}{\mathrm{dt}} = \frac{2}{\rho h_{\mathrm{ref}}} \left(\frac{w_{ref}}{w_{pond}} \right)^{\rho/2} ((Q(w_{\max} - w_{\mathrm{pond}}) + P w_{\mathrm{pond}})(1 - f) - w_{\mathrm{pond}}(E + f I_{\max}))$$

where w_{pond} is the daily fractional flood water coverage, ρ is the geometrical shape factor, w_{max} is the maximum flood water coverage, h_{ref} is the reference flood water depth, w_{ref} is the reference flood water coverage, Q is the runoff, P is the rainfall, I_{max} is the maximum infiltration and $f = \frac{w_{pond}}{w_{max}}$. The daily fractional flood water coverage is aggregated into weekly time series to use in the model