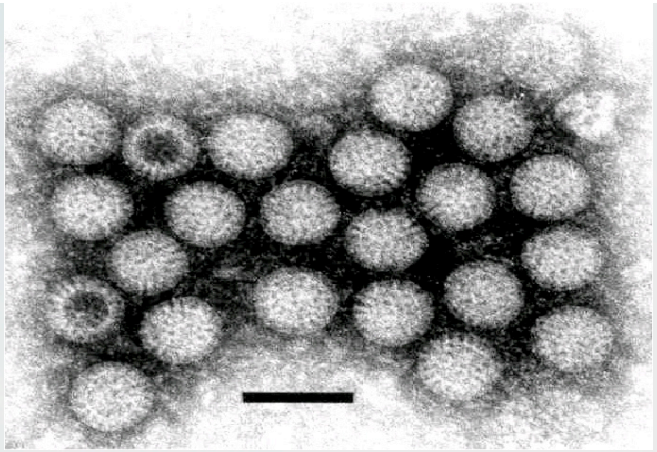
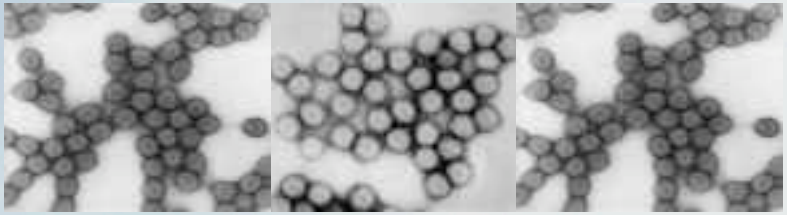


# Rotavirus epidemic & its vaccination

E. Shim[1] , C. Castillo-Chavez[1] , H.T. Banks[2] ,
Z. Feng[3] and M. Martcheva[4]

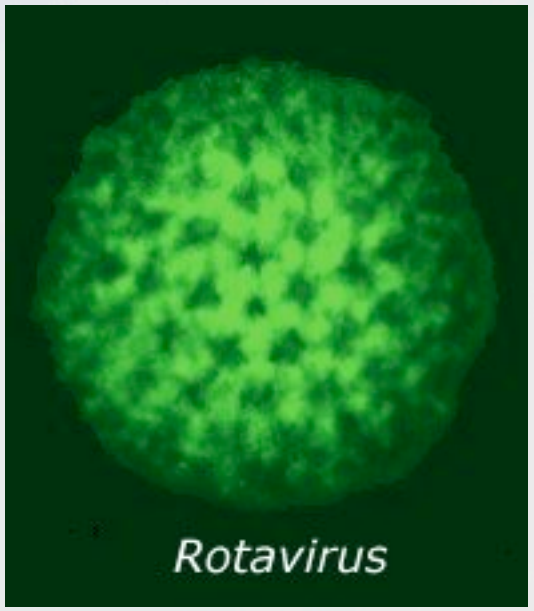
[1]Arizona State University
[2]North Carolina State University
[3]Purdue University
[4]University of Florida

# Goals



- Study seasonality of annual epidemics: Compare two types of vaccines
- Set up an age-structure epidemic model of rotavirus epidemic
- Numerical implementation of an age-structure model.
- Immunological issues: Passive immunity and vaccine

# Morphology of rotavirus




- Family Reoviridae
- Wheel-like distinct appearance under EM (Latin, "rota"=wheel)
- 70-85 nm diameter
- Non-enveloped, double-shelled viruses

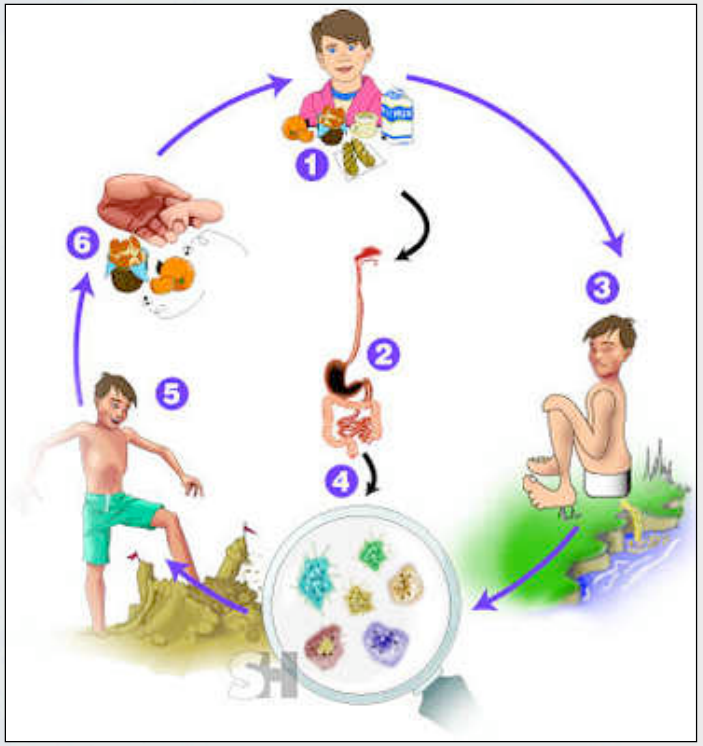
(Picture Source: http://www.sourcemolecular.com/virus2.jpg)

# Epidemiology (1)

- 95% of children worldwide are infected by 3-5 years of age.
- 80% of population have antibody against rotavirus by age 3.
- More frequent in Winter.
- Patterns : annual epidemics occurring from November to April.
  (starting from South western area in November to North east)
- Incidence peaks among children ages 4 to 36 months.
- Symptom : vomiting, diarrhea, dehydration.
  (Repeat infection may occur with milder symptoms)

# Epidemiology (2)

- Latent perios: 24-48 hr.
- Infectious period: 3-7 days.
- Asymptomatic infections are common in adults and older children.
- Primary transmission mode is fecal-oral.
- Ingestion of contaminated food or water and contact with contaminated surfaces

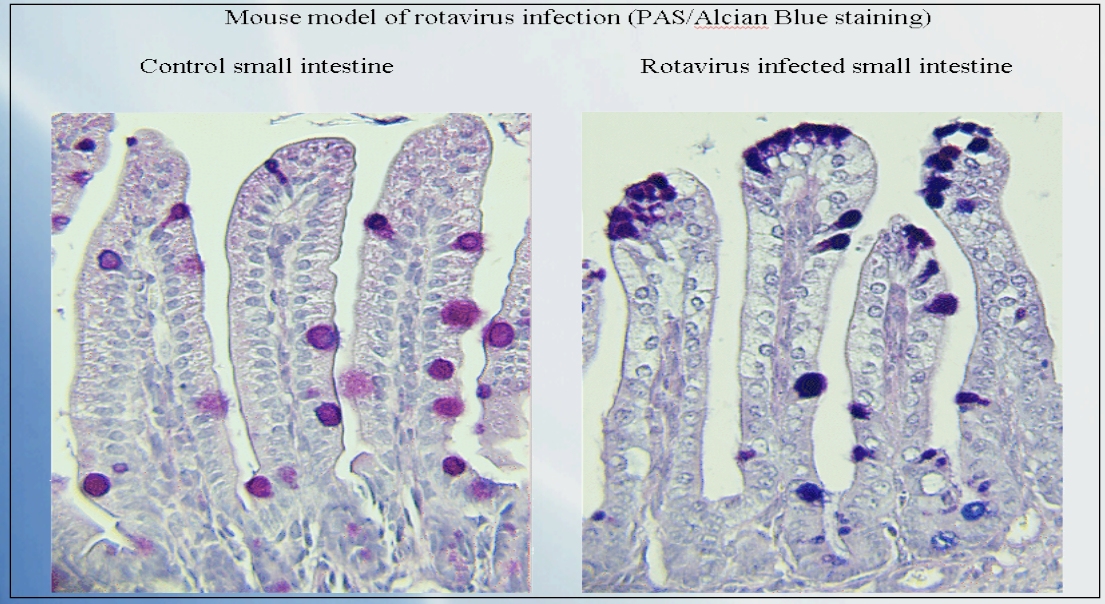


# Replication

- Attached to cell receptors contained sialic acid
- Internalized and uncoated via endolysosomes
- Early transcription by viral RNA polymerase occurs inside sub-viral particle
- Resulted in synthesis of (+) mRNAs and are translated in the cytoplasm.
- Reassortment occurs during Early transcription.
- Secondary transcription occurs in cytoplasm in later infection in a conservative fashion.
- Uncapped non-polyadenylated transcripts
- Particles assemble in the cytoplasm 6-7 h after infection
- Budding from the E.R. into internal spaces & are eventually released when the cell lyses.

# Pathogenesis

- infect upper two-third of duodenal epithelial cell
- infectious particles are released to intestinal lumen and undergo further replication in distal areas
- death of over 600,000 children annually worldwide

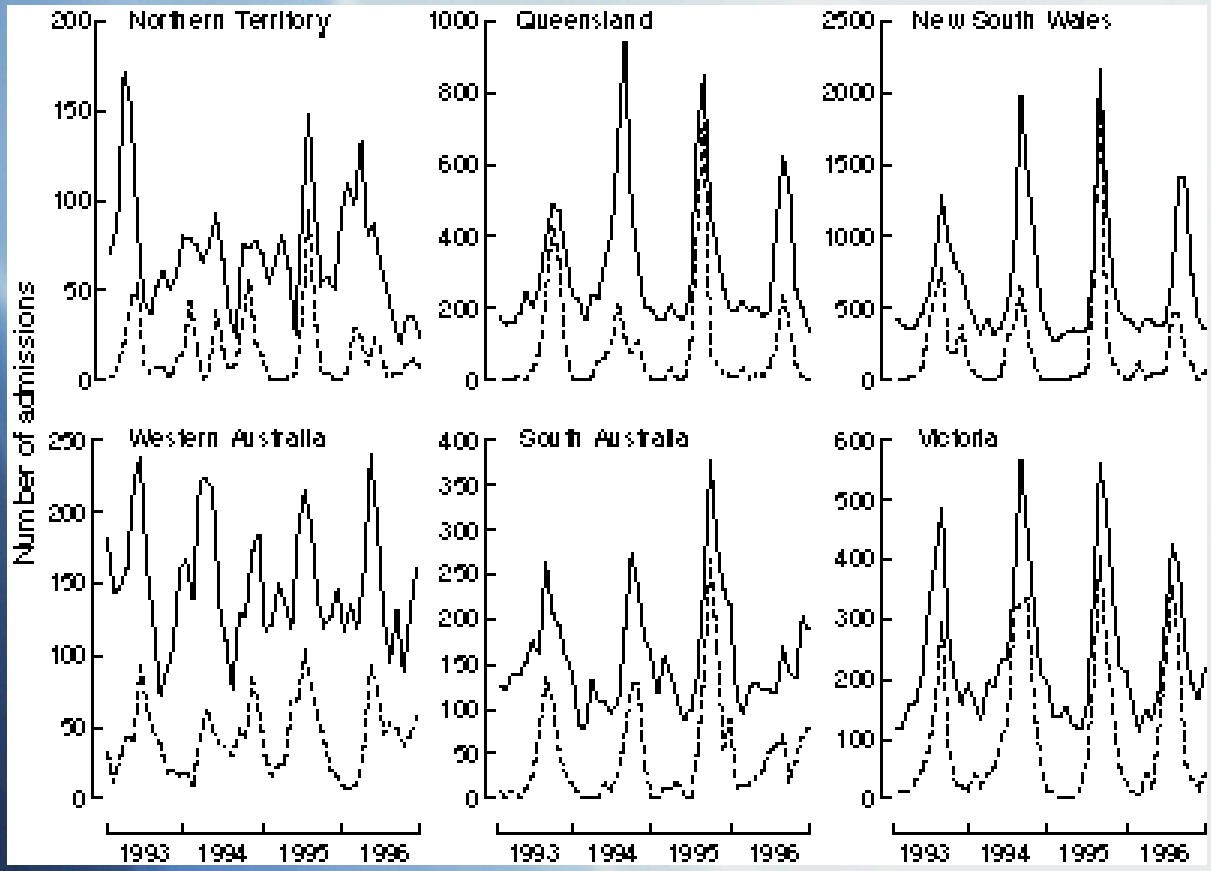



(Picture Source:www.eur.nl/fgg/kgk/gastro/ rotavirus.gif)

# History of Rotavirus vaccine

- Aug 1998: FDA approved Rotashield™, the 1st rotavirus vaccine
- Sep 1998 - July 1998: 15 cases of intussusception cases in were reported to VAERS.
- Sep 1998 - July 1999: CDC reports preliminary data associating Rotashield™ with intussusception and recommends postponing use.
- Oct 1999: Rotashield™ was withdrawn from the market.
- July 2004: Mexican board of Health approved the use in Mexico of Rotarix ™ - GlaxoSimthKlein's new rotavirus vaccine.

# Number of rotavirus positive specimen Australia, 1993-1996

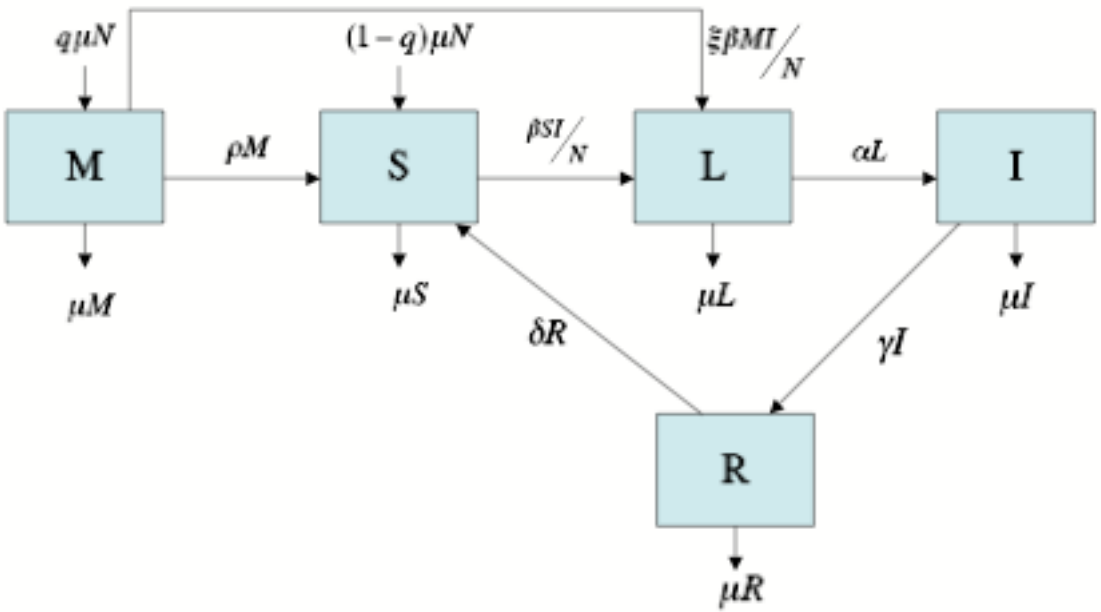



Solid line: hospital admission for acute gastroenteritis in children under five years of age

Dashed line: the number of rotavirus-positive specimens received from participating hospitals in that State, rescaled from the hospital to the State level.

(J.B. Carlin et al. *MJA* 1998; 168: 252-256)

# Seasonal pattern




M: maternal antibodies class
S: Susceptibles
L: Latent
I: Infectious
R: Recovered

## Important parameters

$q$ : *breast feeding rate*

$1-\xi$ : *protection role of breast milk*

$\rho$ : *average breast feeding period*

*where*

$$\beta(t) = \beta_0(1+\beta_1 \cos 2\pi(t-\tau/365))$$

Ref: [2] (By E.Shim, H. T.Banks and C. Castillo-Chavez)

## Model with seasonal pattern of infection

$$M' = q\mu N - \xi\beta MI/N - (\rho + \mu)M,$$
$$S' = \mu[(1-q)N - S] + \rho M - \beta SI/N + \delta R,$$
$$L' = \xi\beta MI/N + \beta SI/N - (\alpha + \mu)I,$$
$$I' = \alpha L - (\mu + \gamma)I$$
$$R' = \gamma I - (\mu + \delta)R$$

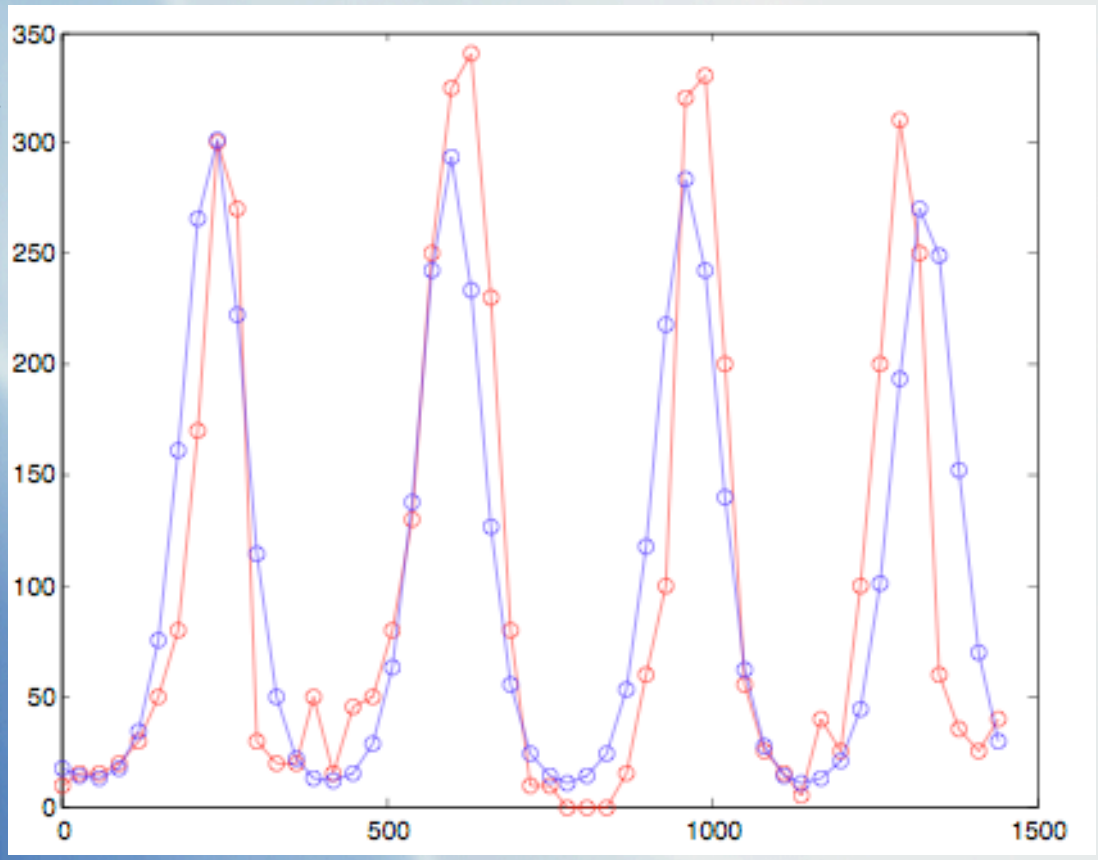
*where*

$$\beta(t) = \beta_0(1 + \beta_1 \cos 2\pi(t - \tau/365))$$

Total population, N(t) = M+S+L+I+R

Ref: [2] (By E.Shim, H. T.Banks and C. Castillo-Chavez)

# Seasonal pattern of rotavirus infection in Victoria, Australia (1993-1996)



# Data fitting

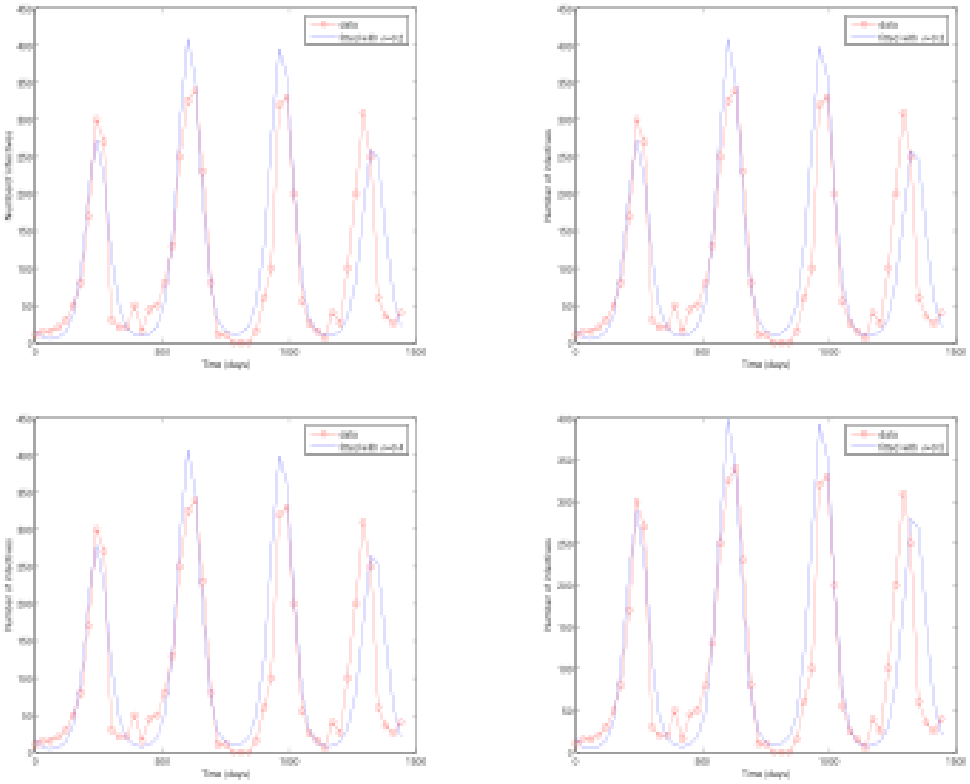


FIGURE 2. Number of infective people of rotavirus in Victoria, Australia, 1993-1996 ([3]) and the fitted graph using seasonality model using various fixed reduction in infection rate due to maternal antibodies. $\xi$ values used: $0.2, 0.3, 0.4$ and $0.5$.

Ref: [2] (By E.Shim, H. T.Banks and C. Castillo-Chavez)

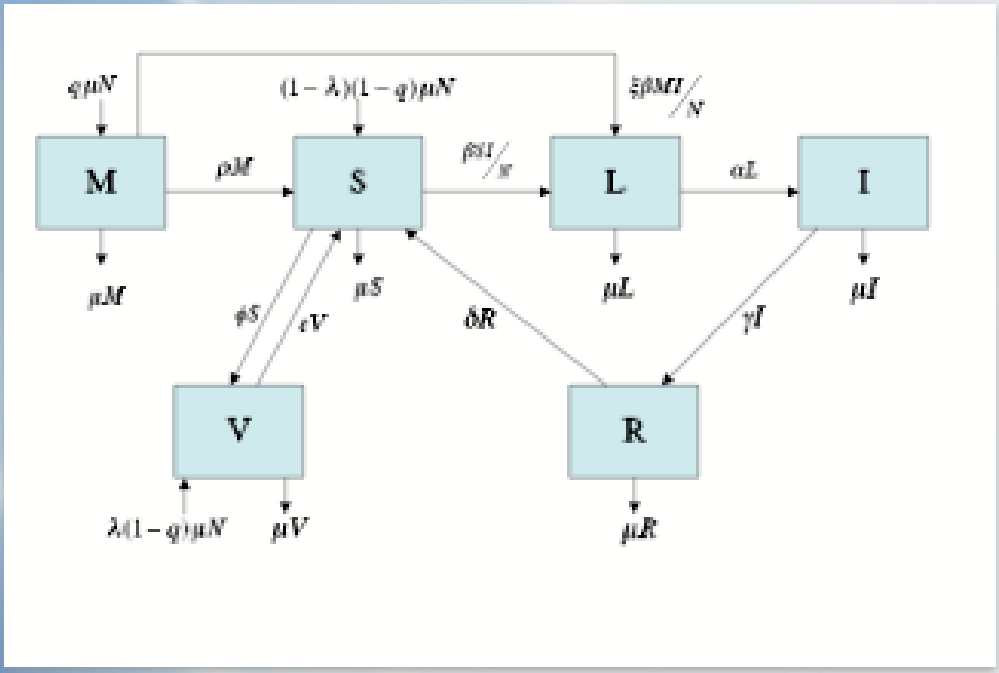
# Estimated parameter values for fitting (using data set in Victoria, Australia, 1993-1996)

TABLE 1. Confidence intervals of estimated parameters when $\xi = 0.2, 0.3, 0.4$ and $0.5$ respectively

| parameters | best-fit values | standard error | 95% confidence intervals |
|---|---|---|---|
| $\rho$ | 0.0003 | 0.0000 | [0.0003, 0.0003] |
| | 0.0001 | 0.0000 | [0.0001, 0.0001] |
| | 0.0000 | 0.0000 | [0.0000,0.0000] |
| | 0.0000 | 0.0000 | [0.0000,0.0000] |
| $\beta_0$ | 0.2077 | 0.0000 | [0.2077, 0.2077 ] |
| | 0.2073 | 0.0000 | [0.2073, 0.2073] |
| | 0.2099 | 0.0000 | [0.2099,0.2099] |
| | 0.2070 | 0.0000 | [0.2070,0.2070] |
| $\beta_1$ | 0.2217 | 0.0300 | [0.1629,0.2805] |
| | 0.2235 | 0.0300 | [0.1647,0.2823] |
| | 0.2266 | 0.0316 | [0.1646,0.2886] |
| | 0.2353 | 0.0332 | [0.1703,0.3003] |
| $\delta$ | 0.1000 | 0.0436 | [0.0146, 0.1854] |
| | 0.1000 | 0.0447 | [0.0123,0.1877] |
| | 0.1000 | 0.0447 | [0.0123,0.1877] |
| | 0.1000 | 0.0469 | [0.0081,0.1919] |
| $\gamma$ | 0.2028 | 0.0000 | [0.2028,0.2028] |
| | 0.2026 | 0.0000 | [0.2026,0.2026] |
| | 0.2055 | 0.0000 | [0.2055,0.2055] |
| | 0.2032 | 0.0000 | [0.2032,0.2032] |
| $\tau$ | 145.6292 | 3.5942 | [138.5846, 152.6738] |
| | 145.8228 | 3.5768 | [138.8123,152.8333] |
| | 145.7564 | 3.5411 | [138.8159, 152.6969] |
| | 145.4982 | 3.5180 | [138.6030,152.3934] |

Ref: [2] (By E.Shim, H. T.Banks and C. Castillo-Chavez)

# Model including "two types" of vaccines model




$\lambda$ : *neonatal vaccination*

$\phi$ : *post – birth vaccination*

$$M' = q\mu N - \xi\beta MI/N - (\rho + \mu)M,$$

$$S' = \mu[(1-\lambda)(1-q)N - S] - \beta SI/N - \phi S + \rho M + \delta R + \varepsilon V,$$

$$L' = \xi\beta MI/N + \beta SI/N - (\alpha + \mu)I,$$

$$I' = \alpha L - (\gamma + \mu)I,$$

$$R' = \gamma I - (\delta + \mu)R,$$

$$V' = \lambda(1-q)\mu N + \phi S - (\varepsilon + \mu)V$$

*with*

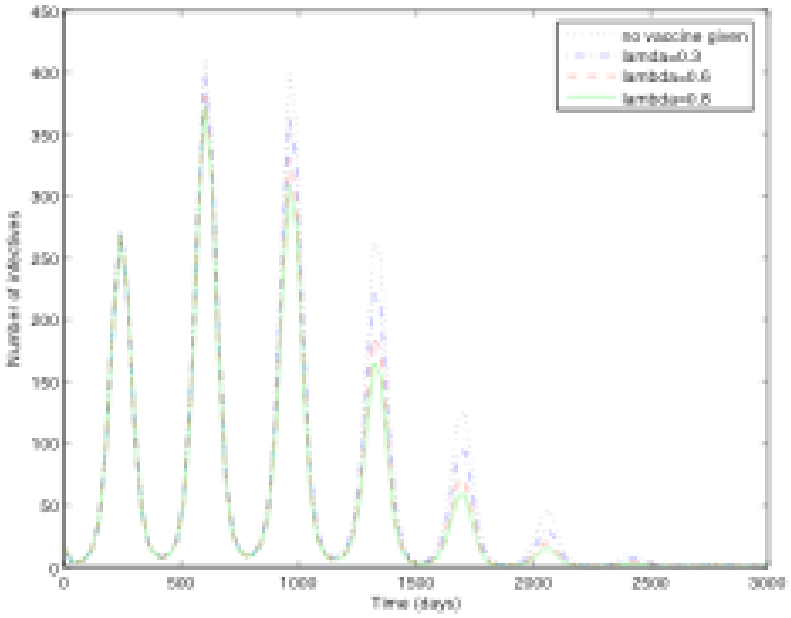
$$N = M + S + L + I + R + V$$

$$\beta = \beta_0[1 + \beta_1 \cos(2\pi(t - \tau))]$$

Ref: [2] (By E.Shim, H. T.Banks and C. Castillo-Chavez)

# Simulated results: comparing effects of two vaccines.

## Neonatal vaccine VS Post-birth vaccine



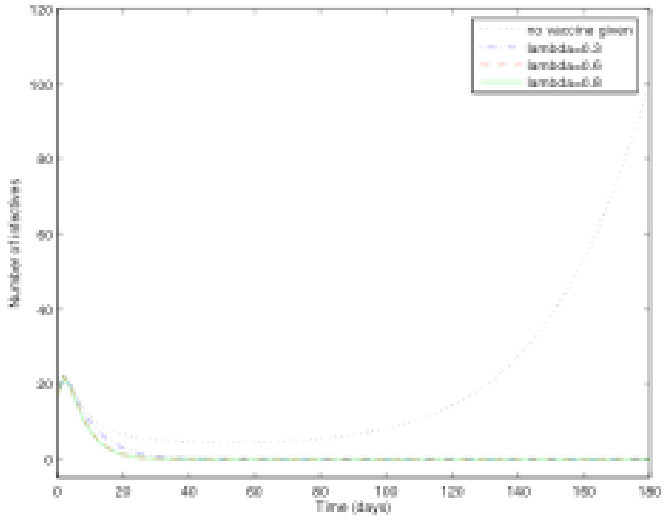




FIGURE 7. Simulated results with various after-birth vaccination rates ($\phi = 0, 0.3, 0.6, 0.8$). Parameters used: $\epsilon = 0.0001$, $\alpha = 0.5$, $\gamma = 0.2$. $\rho$, $\beta_0$, $\beta_1$ and $\delta$ are fixed at best-fit values from Table 1.

Rates (lambda & phi) used: 0.3, 0.6 and 0.8

# Reproductive ratios VS neonatal vaccine rates using various breast feeding duration (2,3,4 and 5 months)

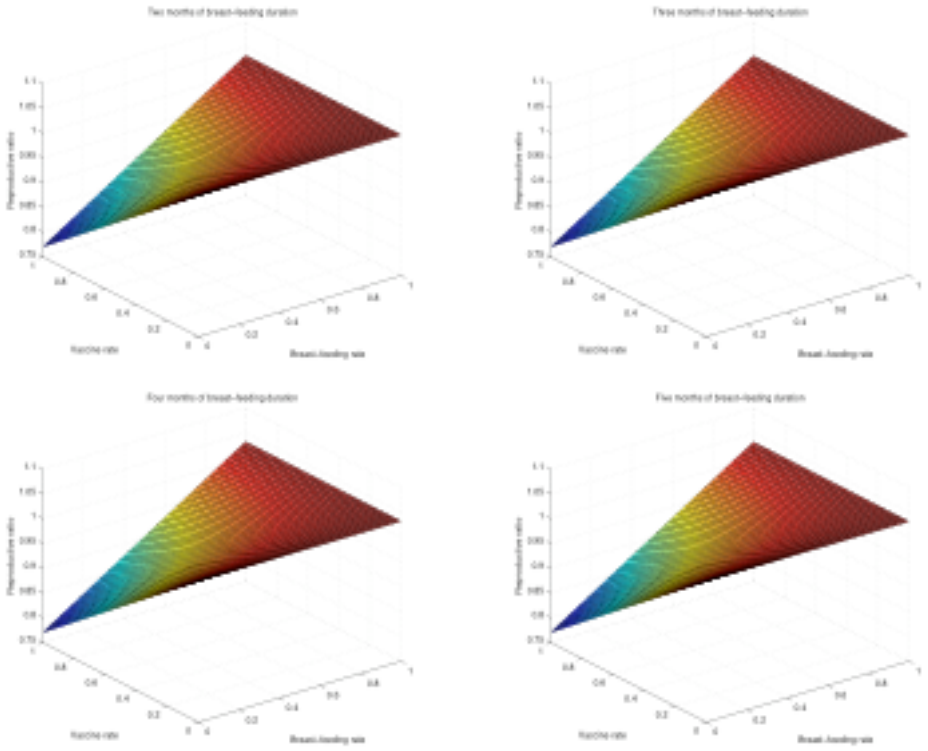


FIGURE 5. Reproductive ratio using neonatal vaccination rate ($\lambda$) and breast-feeding rate ($q$) using various breast-feeding durations (two, three, four and five months)

X-axis: neonatal vaccine rate (lambda)
Y-axis: breast-feeding rate (q)
Z-axis: reproductive ratio

# Reproductive ratios VS post-birth vaccine rates using various breast feeding duration (2,3,4 and 5 months)

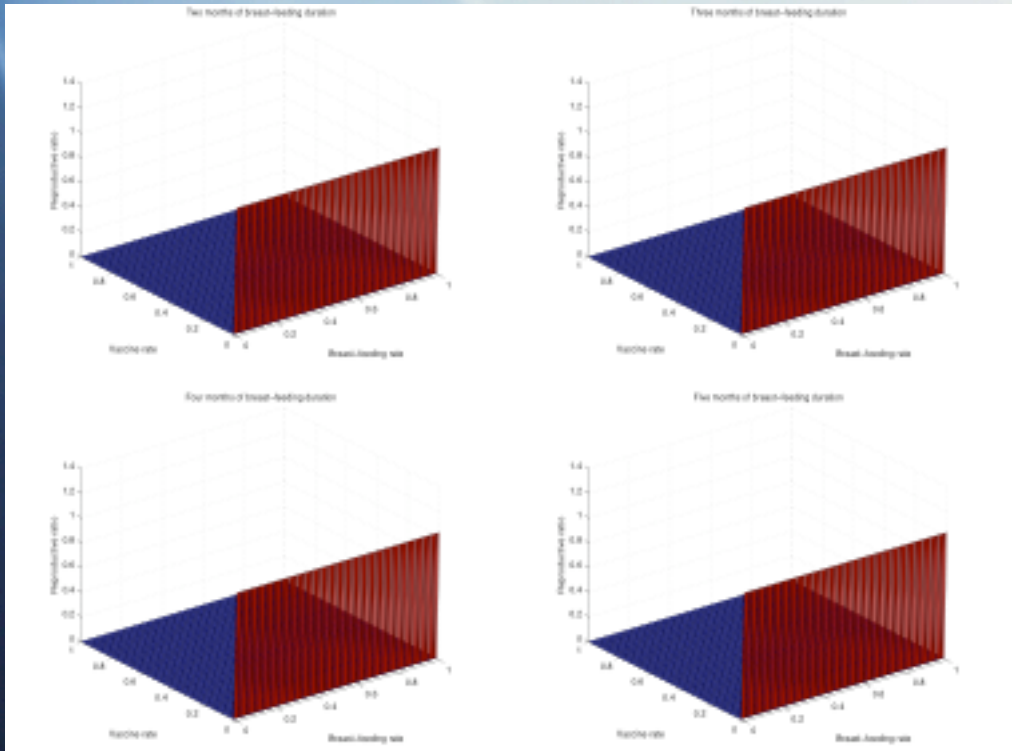
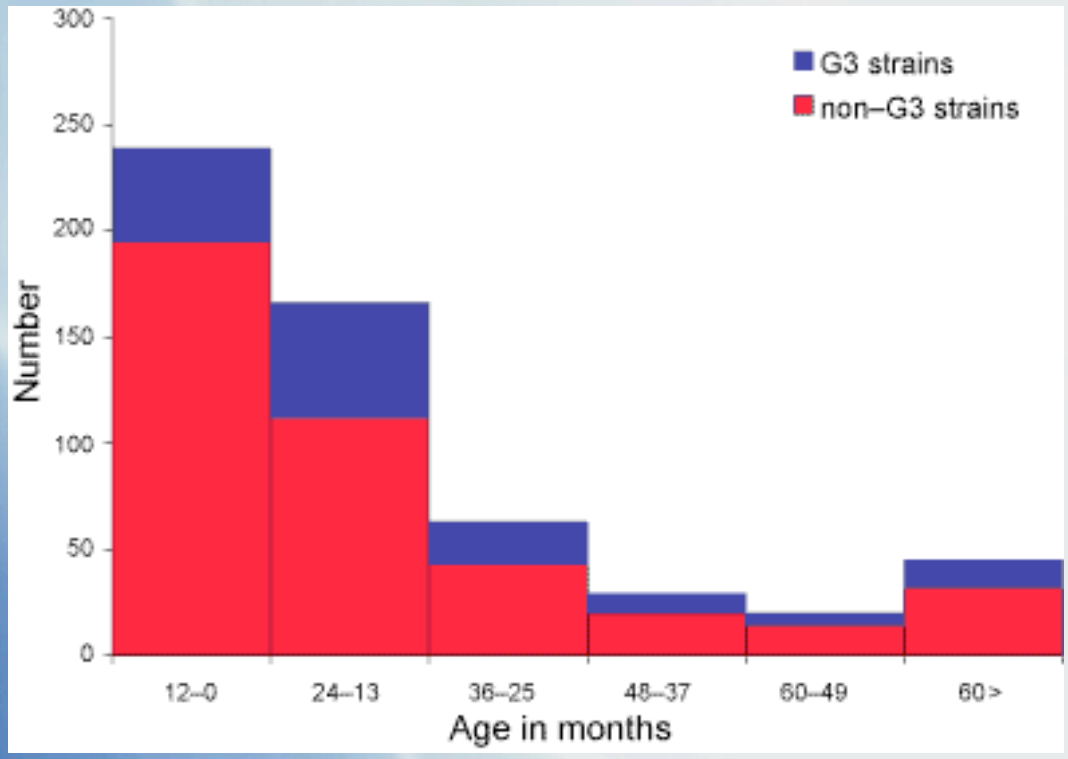


FIGURE 6. Reproductive ratio using post-breast feeding vaccination rate ($\phi$) and breast-feeding rate ($q$) using various breast-feeding durations (two, three, four and five months)

X-axis: post-birth vaccine rate (phi)
Y-axis: breast-feeding rate (q)
Z-axis: reproductive ratio

# Pattern #2: Age distribution of rotavirus cases

## Age distribution versus infecting serotype




C. Kirkwood et al. Report of the Australian Rotavirus Surveillance Program 2003-2004 Comm. Dis. Int. Vol 28 No4.

# Assumptions

- Population is divided into six groups: breast-fed, susceptible, latent, infective, recovered, and vaccinated.
- All newborns enter either breast-fed or susceptible class and we assume maternal antibody protection against infection.
- Portion of susceptible, $\phi(a)$, is vaccinated but vaccine is incomplete and non-permanent.
- Natural immunity (incomplete and non-permanent) gained from previous infection is assumed.
- Age-dependent mixing : contacts between individuals are driven by age-class activity level ad their density.

# *Parameters*

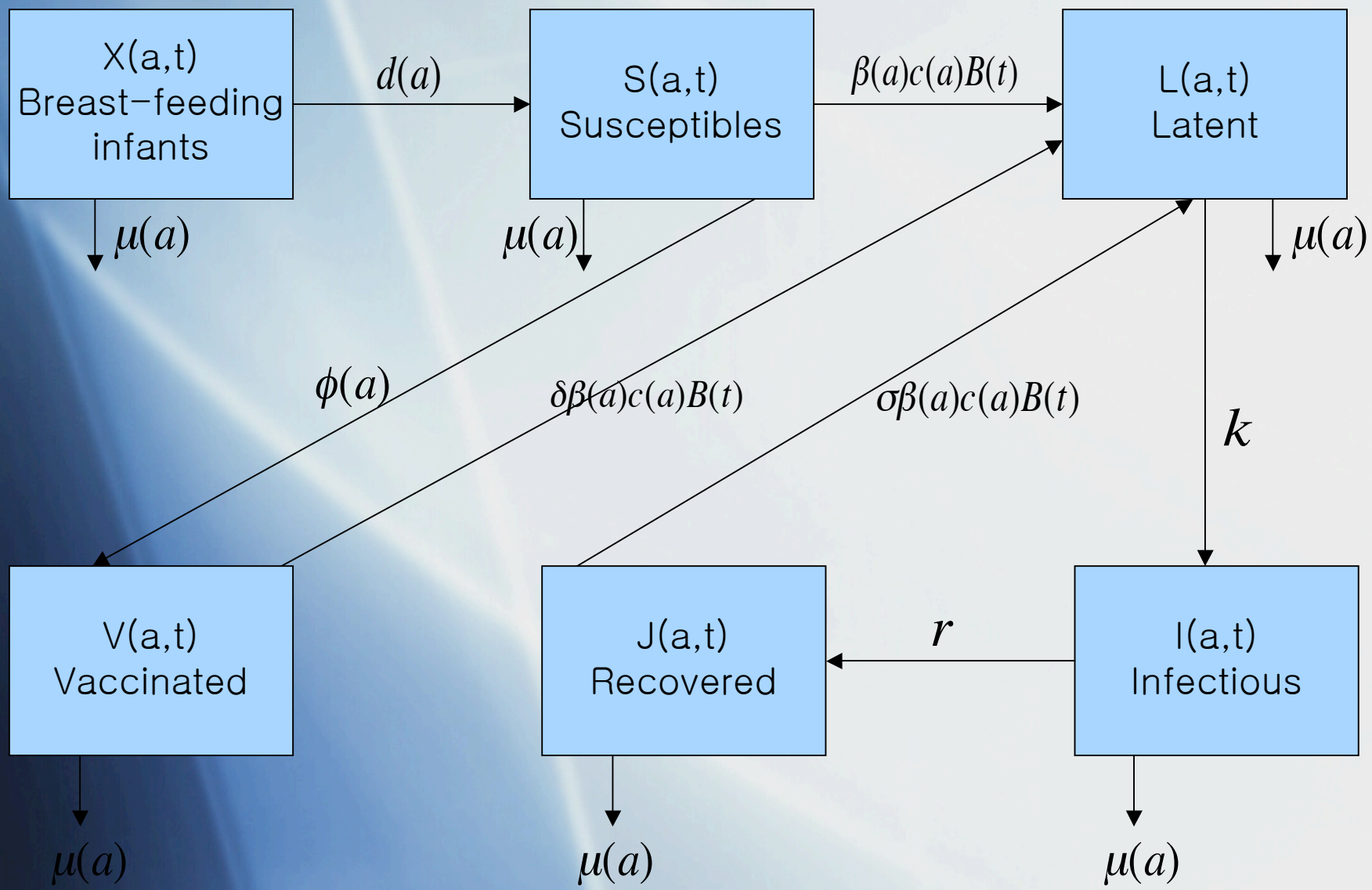
- $\Lambda$: recruitment/birth rate.
- $\beta(a)$: age-specific probability of becoming infected.
- $c(a)$: age-specific per-capita contact rate.
- $\mu(a)$: age-specific per-capita mortality rate.
- $\gamma(a)$: age-specific per-capita recovery rate.
- mixing: $p(t,a,a')$ is probability that an individual of age a has contact with an individual of age a` given that it has a contact with a member of the population

# *Mixing Rules*

- $p(t,a,a`) \geq 0$
- $\int_0^\infty p(t,a,a')da' = 1$
- $c(a)p(t,a,a')n(t,a) = c(a')p(t,a',a)n(t,a')$
- Proportionate mixing:

$$p(t,a,a') = p(t,a') = \frac{c(a')n(t,a')}{\int_0^\infty c(u)n(t,u)du}$$

# Diagram of mathematical model



# Age-structured model of rotavirus infection

$$\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right)X(t,a) = -d(a)X(t,a) - \mu(a)X(t,a)$$

$$\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right)S(t,a) = d(a)X(t,a) - \beta(a)c(a)B(t)S(t,a) - \mu(a)S(t,a) - \phi(a)S(t,a)$$

$$\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right)V(t,a) = \phi(a)S(t,a) - \mu(a)V(t,a) - \delta\beta(a)c(a)B(t)V(t,a)$$

$$\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right)L(t,a) = \beta(a)c(a)B(t)[S(t,a) + \sigma J(t,a) + \delta V(t,a)] - [k+\mu(a)]L(t,a)$$

$$\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right)I(t,a) = kL(t,a) - [r+\mu(a)]I(t,a)$$

$$\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right)J(t,a) = rI(t,a) - \sigma\beta(a)c(a)B(t)J(t,a) - \mu(a)J(t,a)$$

$$B(t) = \int_0^\infty \frac{i(t,a')}{n(t,a')}p(t,a,a')da'$$

where

$$p(t,a,a') \geq 0, \qquad \int_0^\infty p(t,a,a') = 1,$$

$$c(a)n(a,t)p(a,a',t) = c(a')n(a',t)p(a',a,t)$$

Ref: [1] (By E.Shim, Z. Feng, Z. Martcheva and C. Castillo-Chavez)

# Reproductive Ratio (1)

- What is basic reproductive number, $R_0$ ?

  the expected number of newly infected that one infectious individual will produce during his (or her) period of infectiousness in a large, 100% susceptible population

$$\Re(\phi) = \int_0^\infty \int_0^\infty \frac{k}{r-k} p_\infty(\tau + h)[e^{-k\tau} - e^{-r\tau}]\beta(h)c(h)[s^*(h) + \delta v^*(h)]dhd\tau$$

where

$$s^*(a) = qe^{-\int_0^a \phi(\tau)d\tau} \int_0^a d(h)e^{\int_0^h \phi(\tau)-d(\tau)d\tau} dh + (1-q)e^{-\int_0^a \phi(\tau)d\tau},$$

$$v^*(a) = \int_0^a \phi(h)s^*(h)dh,$$

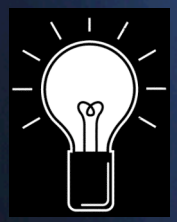
Ref: [1] (By E.Shim, Z. Feng, Z. Martcheva and C. Castillo-Chavez)

# Basic Reproductive Ratio (2)

Now let's consider without vaccination!

$$R_0 = \int_0^\infty \int_0^\infty \frac{k}{r-k} p_\infty(\tau + h)[e^{-k\tau} - e^{-r\tau}]\beta(h)c(h)[1 - q^{-dh}]dhdr$$

$$\frac{\partial R_0}{\partial q} < 0 \quad \text{and} \quad \frac{\partial R_0}{\partial (1/d_0)} < 0$$



When every new born is breast-fed (q=1) or when the length of mean antibody protection period increase we see reduction in basic reproductive ratio.

Ref: [1] (By E.Shim, Z. Feng, Z. Martcheva and C. Castillo-Chavez)

# Local stability analysis of infection-free non- uniform steady state distributions

- Theorem 1. The infection-free steady state distribution is l.a.s. if $R(\phi) < 1$.

Proof. We introduce the characteristic equation:

$$\Re(\phi) = \int_0^\infty \int_0^\infty \frac{k}{r-k} p_\infty(\tau + h)[e^{-k\tau} - e^{-r\tau}]\beta(h)c(h)[s^*(h) + \delta v^*(h)]dhd\tau$$

Note that it has negative real solution of $\lambda$ if and only if G(0)<1 ( that is, $R(\phi)$< 1) since

$$G'(\lambda) < 0, \quad \lim_{\lambda \to \infty} G(\lambda) = 0, \quad \lim_{\lambda \to -\infty} G(\lambda) = \infty.$$

Similarly it has a positive real solution $\lambda$ if and only if G(0)>1 (that is, $R(\phi)$ > 1). Thus the infection free steady distribution is l.a.s. if $R(\phi)$<1 and unstable otherwise.

Ref: [1] (By E.Shim, Z. Feng, Z. Martcheva and C. Castillo-Chavez)

# Global stability analysis of infection-free non- uniform steady state distributions

- Theorem 2. The infection-free steady state distribution is g.a.s. if $R_0$ < 1 where

$$R_0 = \int_0^\infty \int_0^\infty \frac{k}{r-k} p_\infty(\tau + h)[e^{-k\tau} - e^{-r\tau}]\beta(h)c(h)[1 - q^{-dh}]dhdr$$

- Theorem 3. There exists endemic non-uniform steady state distribution if $R(\phi)$ > 1.

Ref: [1] (By E.Shim, Z. Feng, Z. Martcheva and C. Castillo-Chavez)

# Three doses and waning immunity?

- Keep breast-fed class: [1-D(a)]X(a,t)
- Susceptible class: D(a)X(a,t)
- Primary infection: I(a,t)
- Subsequent infection: $I_m(a,t)$

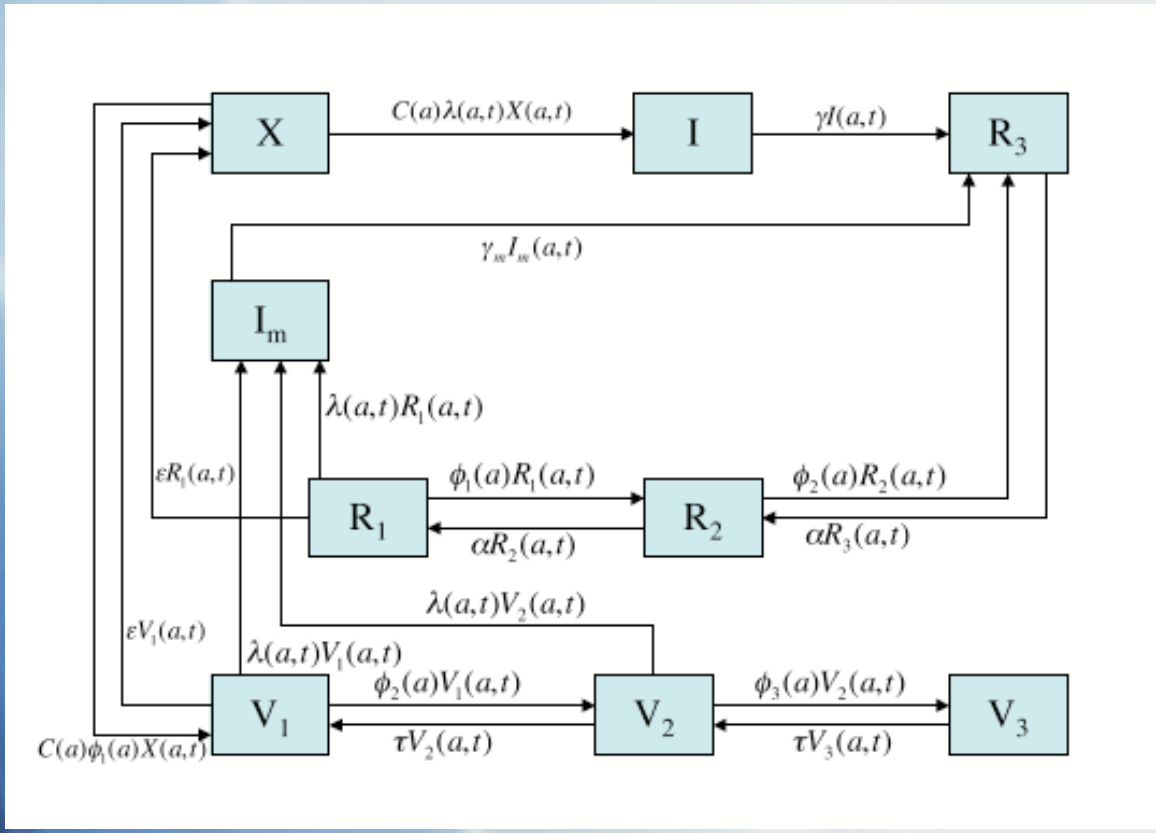

- Recovered class with waning immunity:

  $R_3(a,t)$ --> $R_2(a,t)$ --> $R_1(a,t)$

  (strong)---------->(weak)

- Multiple doses: $V_1(a,t)$ $V_2(a,t)$ $V_3(a,t)$

# Model involving subsequent infection and multiple doses of vaccine.




1. Boosting immunization + natural immunity
2. Brest-fed infants: protected & non-vaccinated

# Discretization on each age group

$$X_i = \int_{a_{i-1}}^{a_i} X(a',t)da', \qquad I_i = \int_{a_{i-1}}^{a_i} I(a',t)da', \qquad I_{mi} = \int_{a_{i-1}}^{a_i} I_m(a',t)da',$$

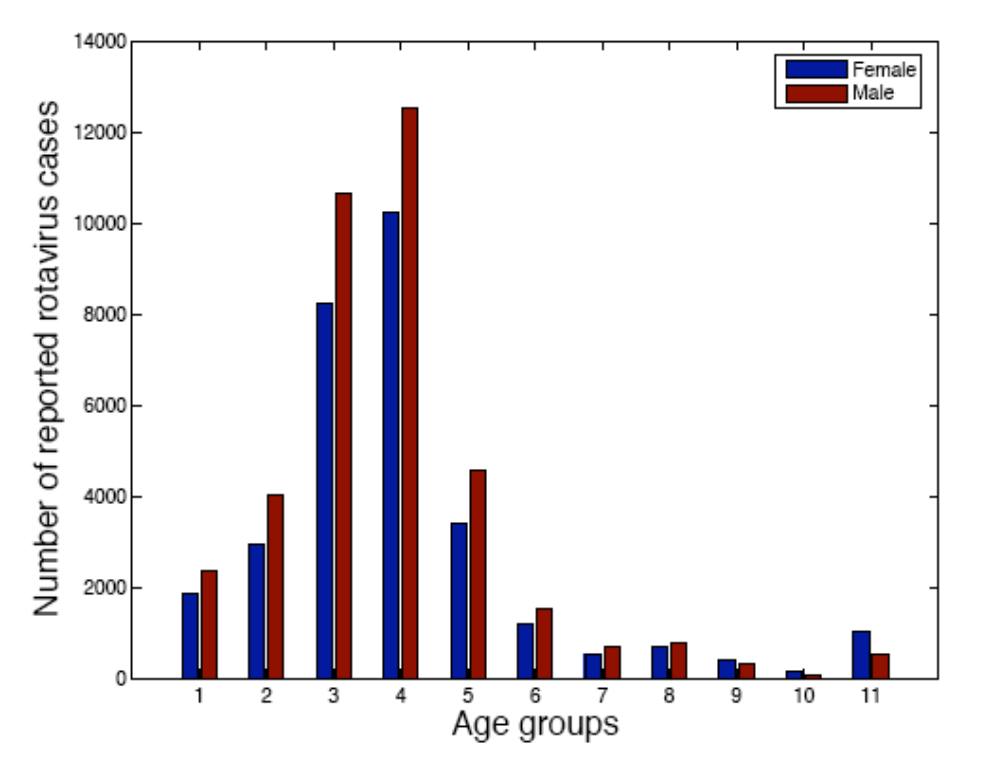
$$R_{1i} = \int_{a_{i-1}}^{a_i} R_1(a',t)da', \qquad R_2 = \int_{a_{i-1}}^{a_i} R_2(a',t)da', \qquad R_{3i} = \int_{a_{i-1}}^{a_i} R_3(a',t)da',$$

$$V_{1i} = \int_{a_{i-1}}^{a_i} V_1(a',t)da', \qquad V_{2i} = \int_{a_{i-1}}^{a_i} V_2(a',t)da', \qquad V_{3i} = \int_{a_{i-1}}^{a_i} V_3(a',t)da'.$$

And do normalization! i.e. divide them by the total number of individuals of age between a_(i-1) and a_(i)

$$N_i(t) \equiv \int_{a_{i-1}}^{a_i} u(a,t)da = e^{qt} \int_{a_{i-1}}^{a_i} A(a)da := e^{qt} P_i$$

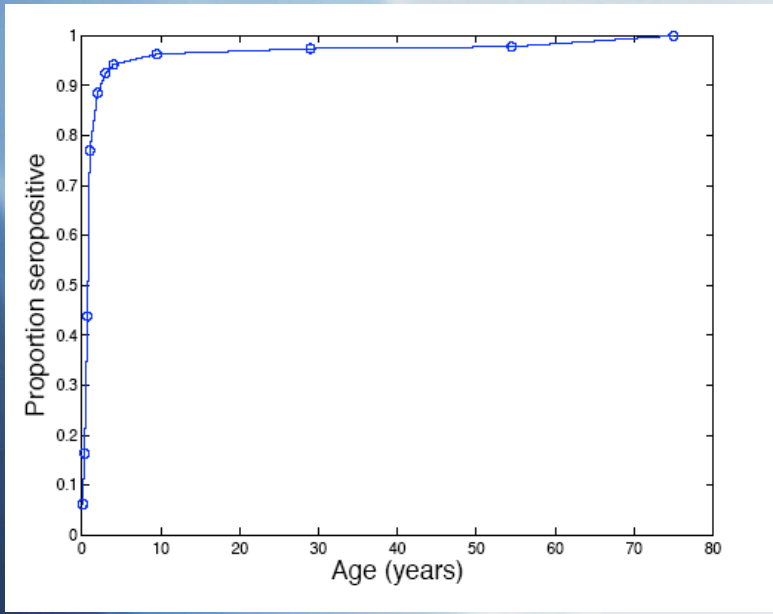
# Estimation of force of infection (1)

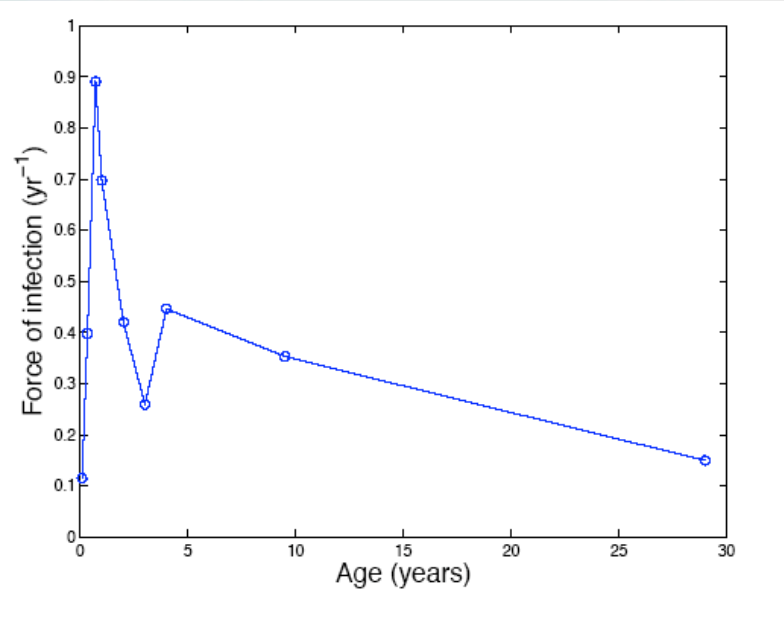



$$\lambda_i = -\ln\left[\frac{1-p_{i+1}}{1-p_i}\right],$$

- p_(i) = proportion of individuals of age “i” who have experienced infection

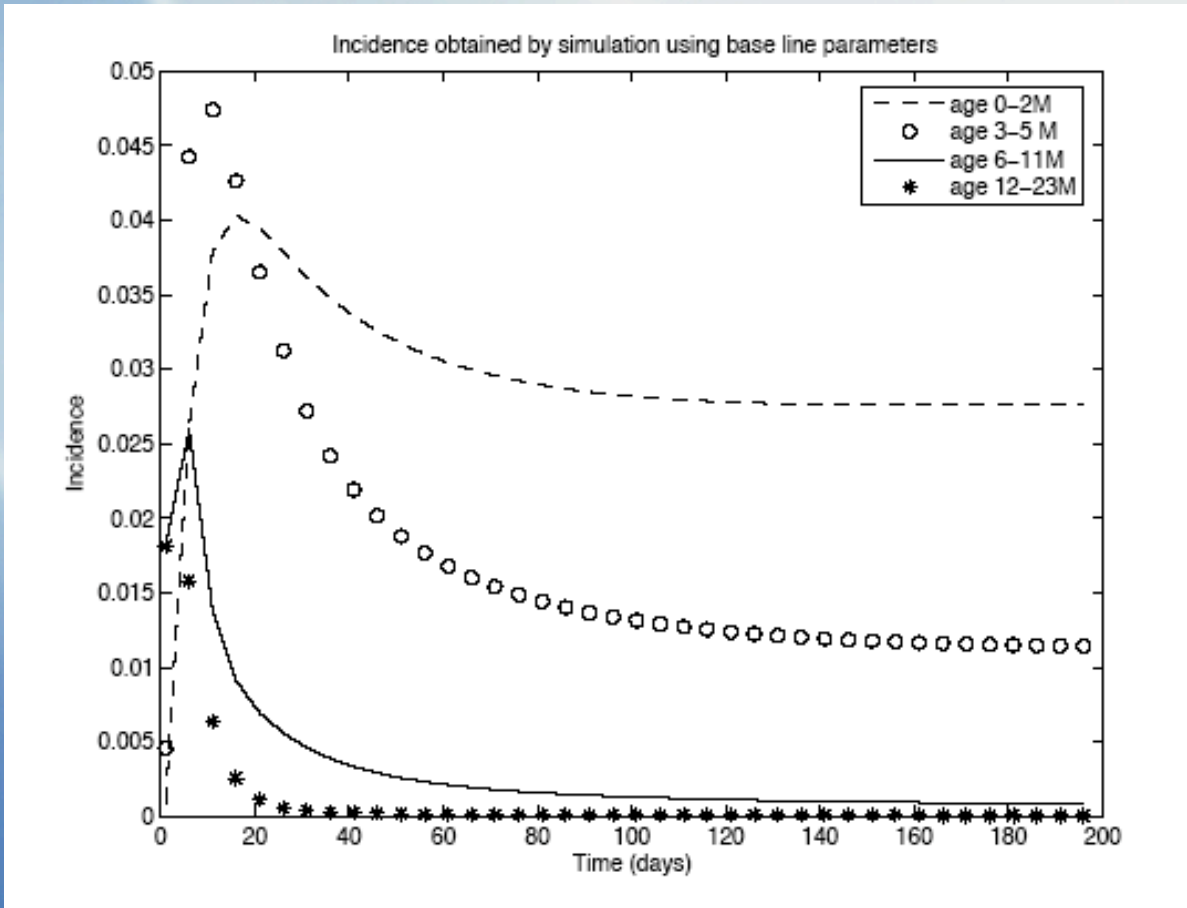
# Estimation of force of infection (2)



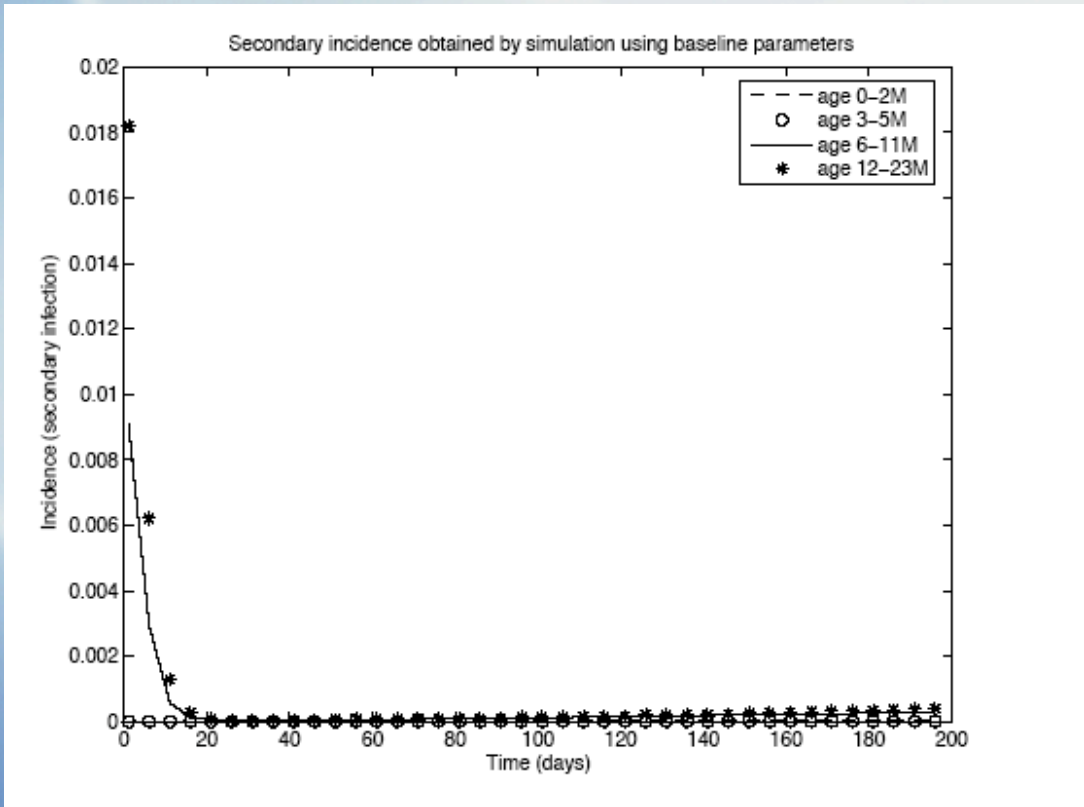

- Force of infection among younger ages are higher, especially under three years old…

# Some simulated work (1)



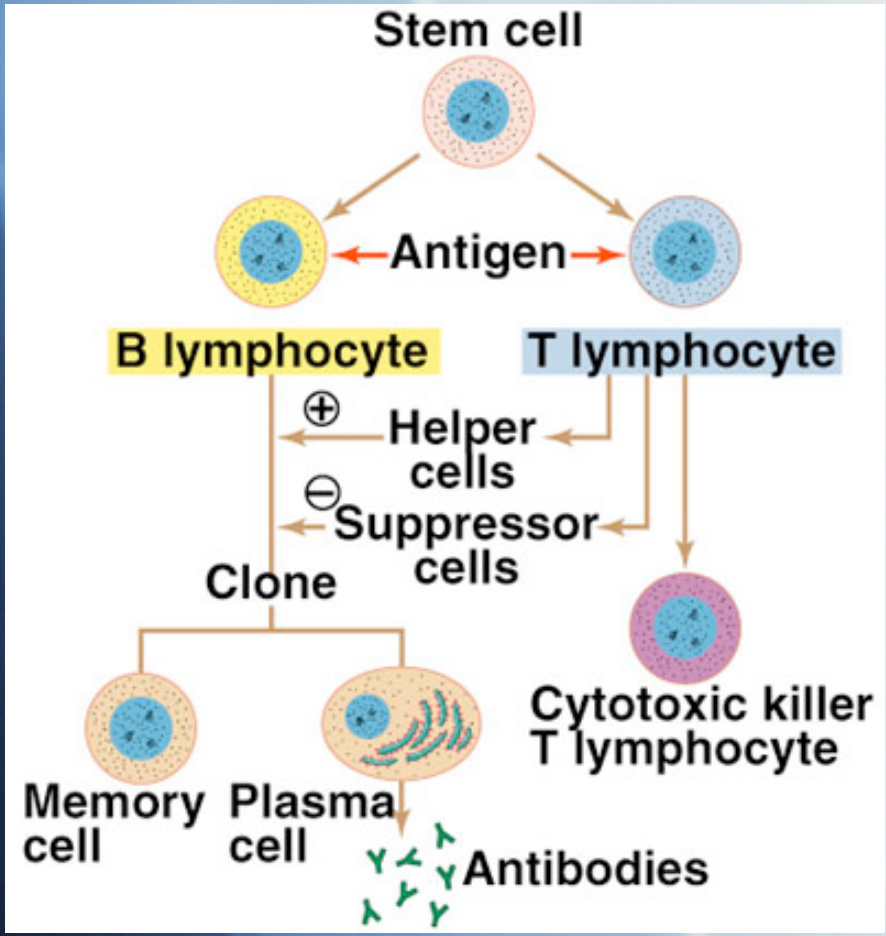

- Primary infection incidence rates of each age group

# Some simulated work (2)



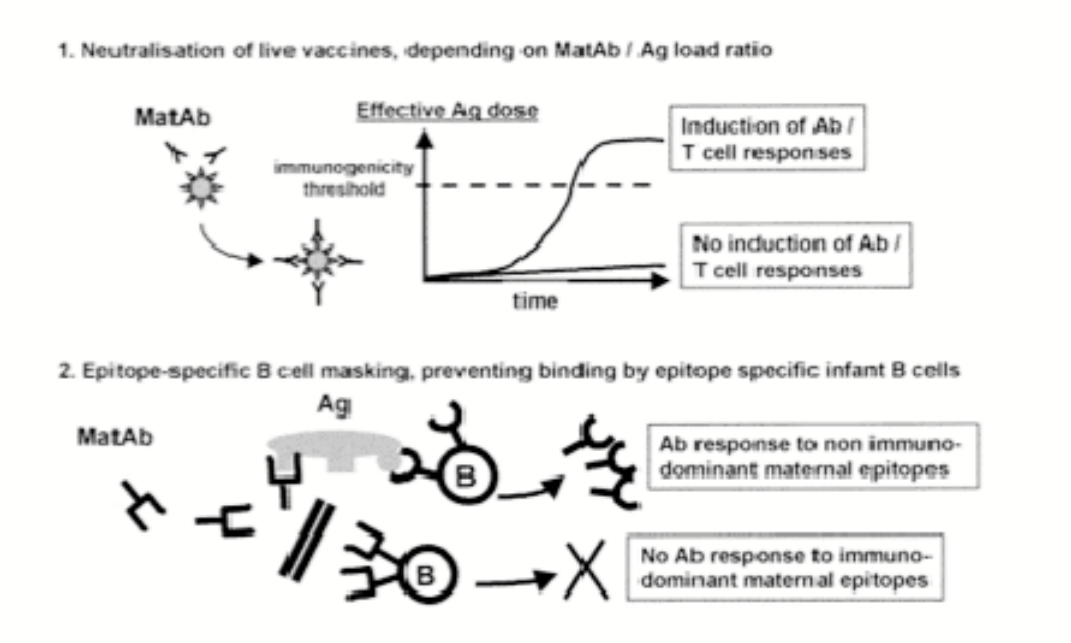

- Subsequent infection incidence using base line parameters for each age group (among infants)

# Immunological issues (1)




- Upon activation of B cells by antigens, B cells go through proliferating phase to make its own clones
- Finally humoral immunity results in producing short lived plasma cells (making Ab) and some B cells become memory B cells

# Immunological issues (2)




- Dual effects of maternal antibodies
- Protection: they provide some level of protection against rotavirus infection
- Suppressive effect: But higher pre-vaccine Ab titers result in lower rates of sero-conversion rates after vaccination

# Conclusion

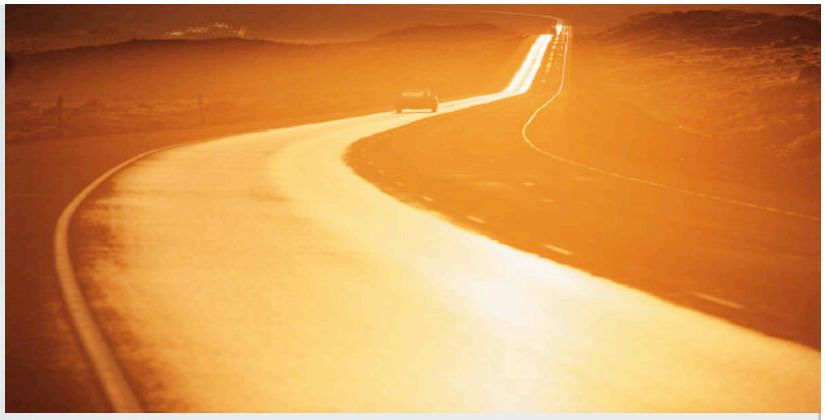
- Seasonal pattern of epidemic curve
- Vaccine issues : post-birth vaccine is more efficient than neonatal vaccine.
- Local/ Global result using basic reproductive ratio
- Age-structure model: find "optimal" age window for vaccination
- Breast-feeding: longer /more breast feeding help to eradicate rotavirus infection
- Maternal antibody : its protection role and relation to immunization schedule is important.

# References


- [1] E. Shim, Z. Feng, M. Martcheva and C. Castillo-Chavez. An age-structured model of rotavirus with vaccination. (submitted to JMB)

- [2] E. Shim, H.T.Banks and C. Castillo-Chavez. Seasonality of rotavirus infection with its vaccination. AMS contemporary book series. (to appear)

# Future Directions



- PDE-> ODE for simulated works of three doses model. (explore the impact of 2,4 and 6 months old schedule of Rotateq / Rotarix)
- Study Geographic pattern and find driving forces (weather, humidity, travel? )
- Impact of maternal antibodies is always important

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