

Faut-il un vaccin anti-CMV?

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Mode d'acquisition

- Transmission par le sang, les sécrétions génitales, le lait maternel, , la salive et les urines
- Excrétion asymptomatique
- Deux pics d'acquisition ?

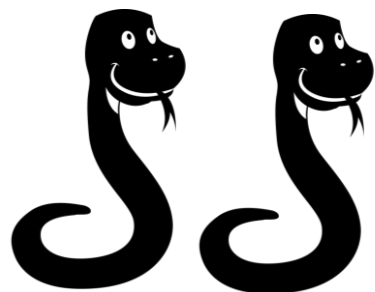


Contamination/pouvoir pathogène



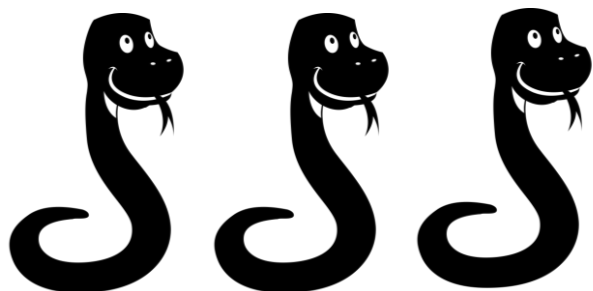
Primo-infection

Cheeran et col Clin Microbiol Rev 2009



Réinfections

Yamada et col J Infect Chemother. 2018
Mack et col Front Pediatr. 2017



Réactivations

Ando et col Biol Blood Marrow Transplant. 2019

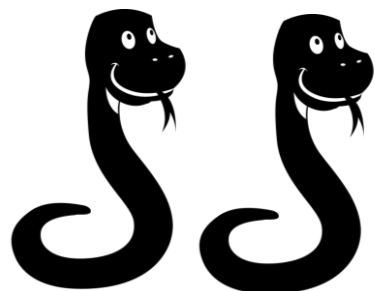
Contamination/pouvoir pathogène



Primo-infection

50%
des infections congénitales

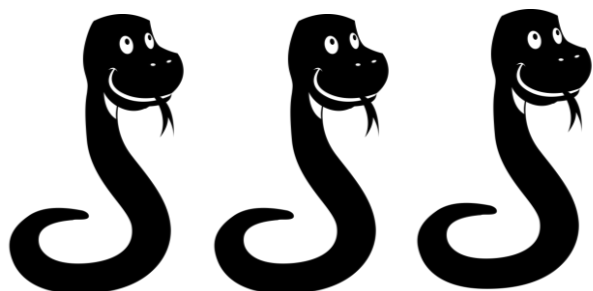
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Réinfections

50%
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Réactivations

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la morbidité: une pour tous



la morbidité: une pour tous



première cause d'infection congénitale : 0,7% (0,25 à 2%)

12,7% sont symptomatiques

12 % des asymptomatiques développent des

Evolution imprévisible Pas de traitement pendant la grossesse

deuxième cause de surdit 

15% de MFIU

Pr maturit  et RCIU sous estim e

r le des infections secondaires et des r activations sous estim es :

Primo: 30-50%

R activation et r infection: 50%

Le taux et la gravit  des s quelles sont identiques au cours des infections secondaires

Griffiths et col *J Pathol* 2015
Kenneson A *Rev Med Virol* 2017
Kimberlin et col. *NEJM* 2015
Boppana et col, *NEJM* 2001

la morbidité: une pour tous

Patients immunodéprimés:

Greffés d'organes
Greffés de moelle
VIH stade SIDA

Réactivation ou contamination

Griffiths et col *J Pathol* 2015



Pathologies:

Pulmonaire
Digestive
Ophtalmologique

Chaque événement: +30% du coût
de la greffe

Hill et col, *NEJM* 1964

Webster *Lancet* 1989

Deayton *Lancet* 2004

Robin et col *BMC infect Dis.* 2017

la morbidité: une pour tous

Facteur de risque cardio-vasculaire?

Mortalité précoce?

Activation T8

Efficacité moindre des vaccins anti-grippaux et anti-pneumocoques?

Rubin et col *J Am Med Assoc* 1989
Simanek et col *Plos One* 2011
Pawelec G et col *Rev Med Virol* 2009



la morbidité: une pour tous

Actifs

- **Accident professionnel**
25-40% des personnes travaillant dans la petite enfance seront infectés pendant leur première année de travail
- **Personnel soignant**
Mesures préventives
Peu de déclarations

Mujzicika et col Eur J Clin Microbiol Infect Dis
2014

Nienhaus et col Int J Environ Res Public Health
2018

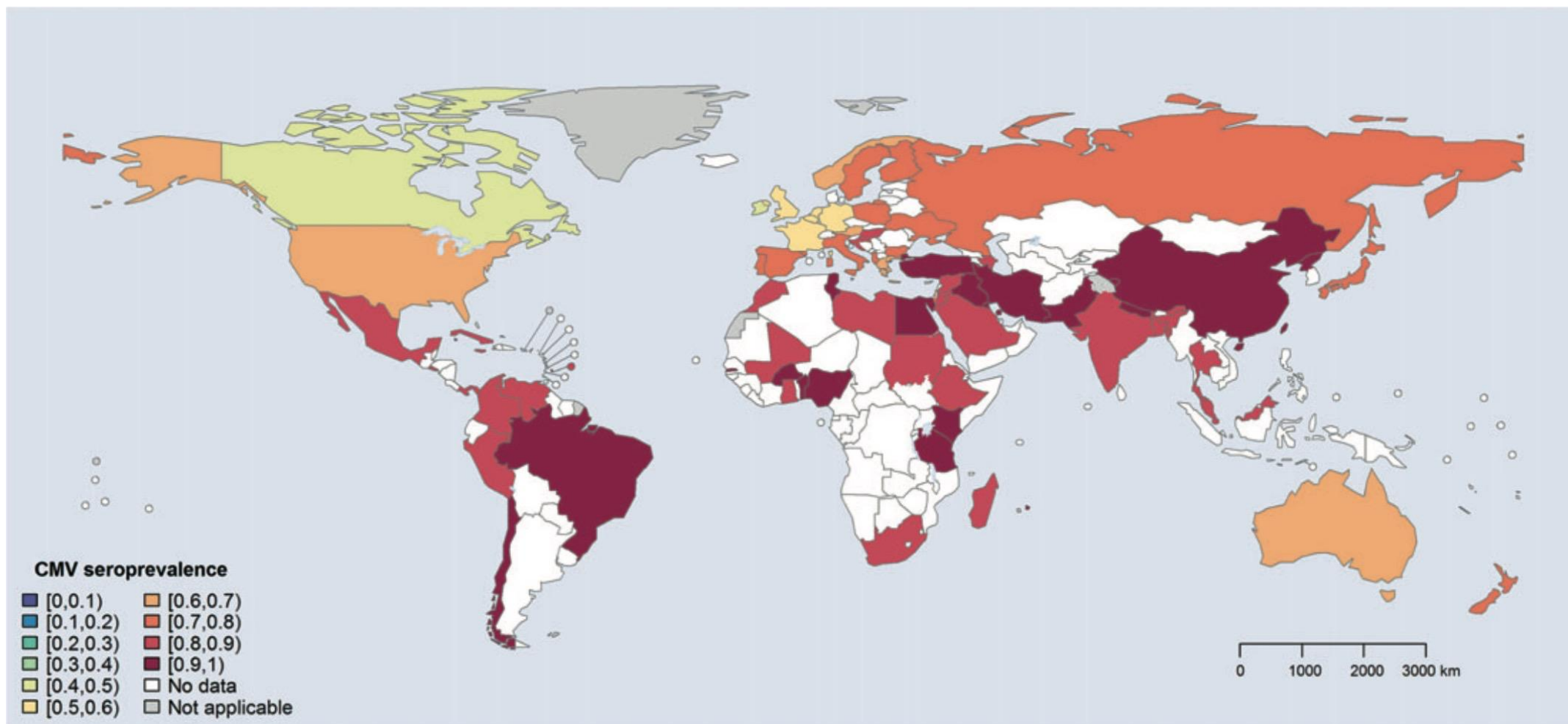
Stratinzger et col GMS Hyg Infect Control 2016



Actifs: Conséquences
Arrêt de travail prolongé?
'syndrome post infectieux?
Coût?

Pas de littérature, 2019

Epidémiologie générale

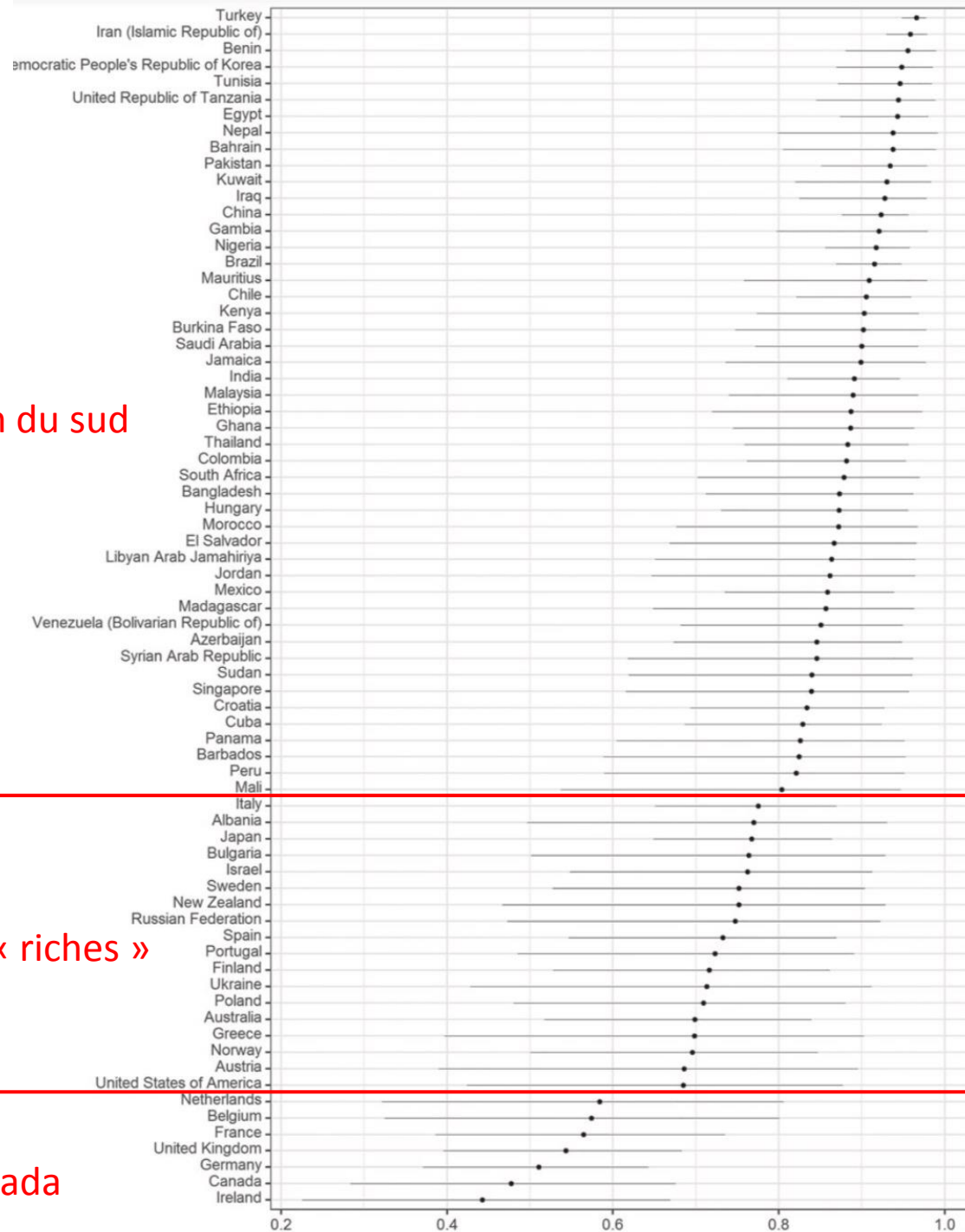


Epidémiologie générale

Afrique+Asie+Am du sud

Europe+pays « riches »

Europe et Canada



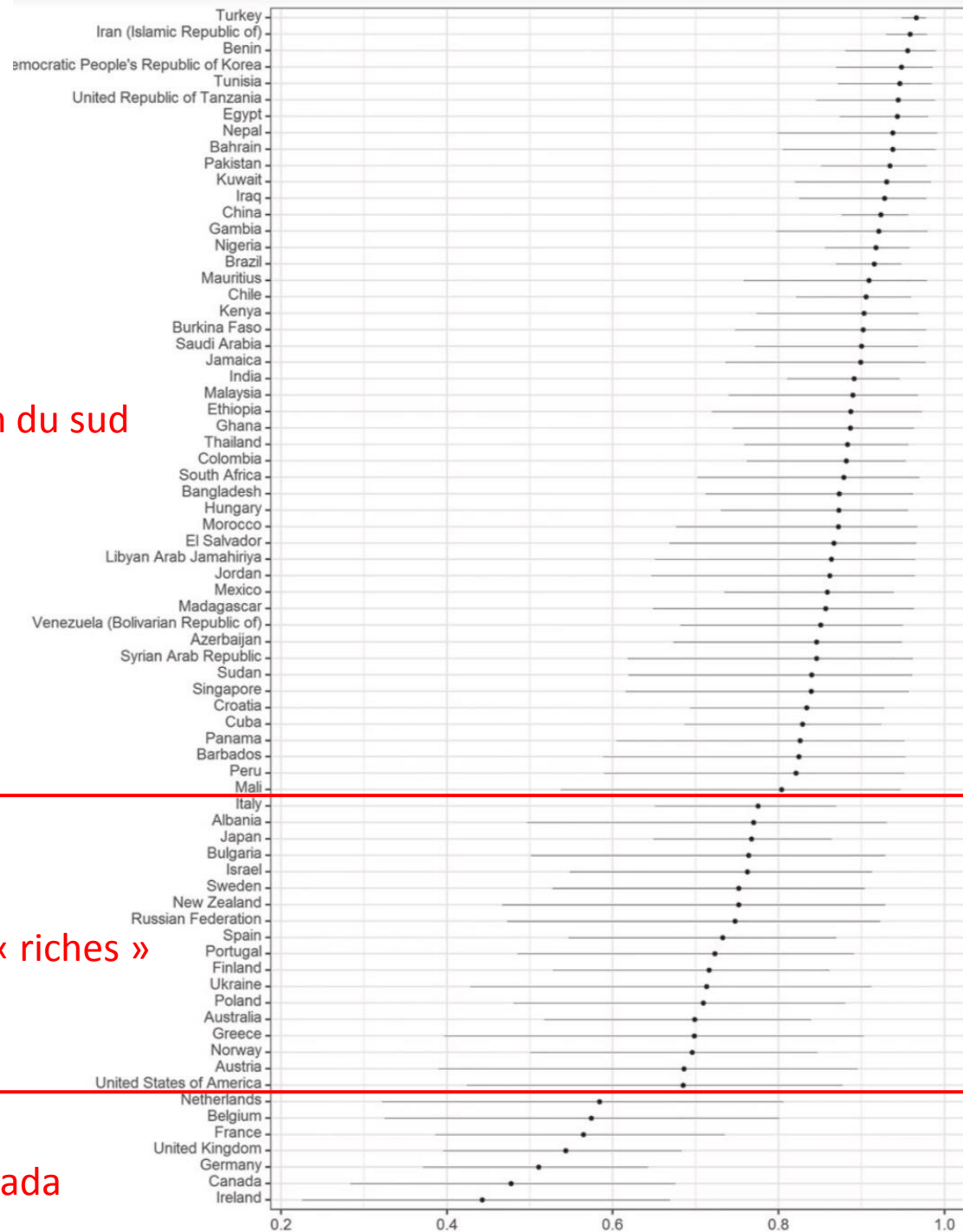
Epidémiologie générale

Grande variabilité mais maladie « fréquente »

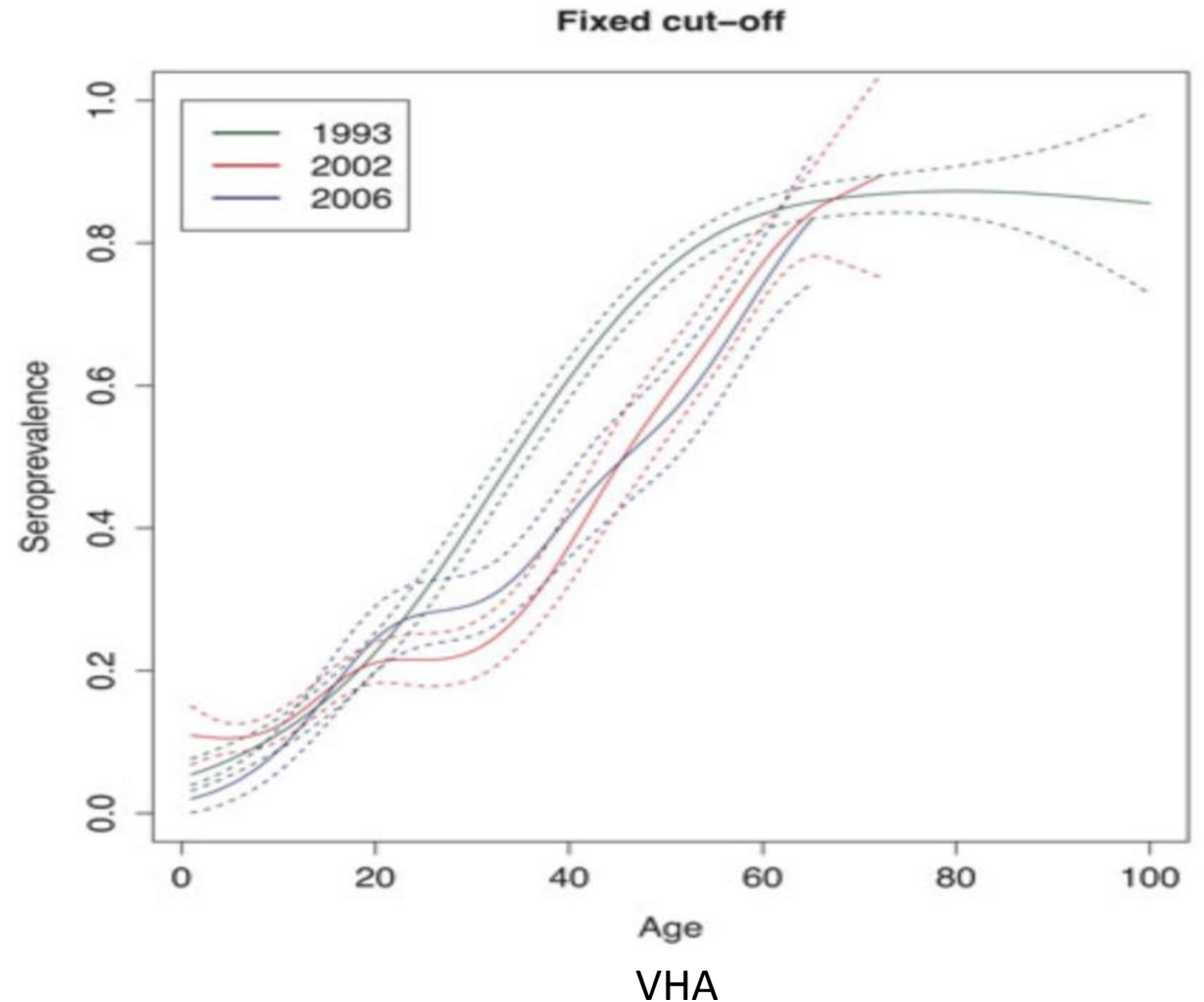
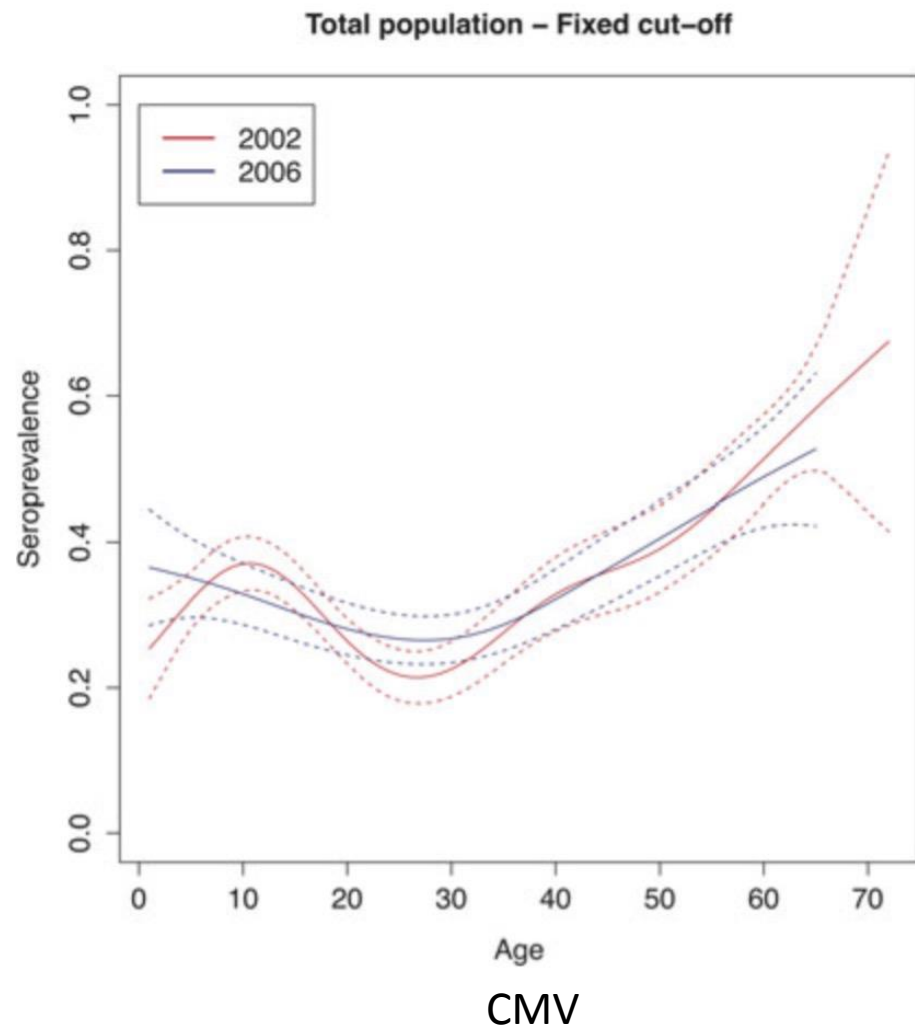
Afrique+Asie+Am du sud

Europe+pays « riches »

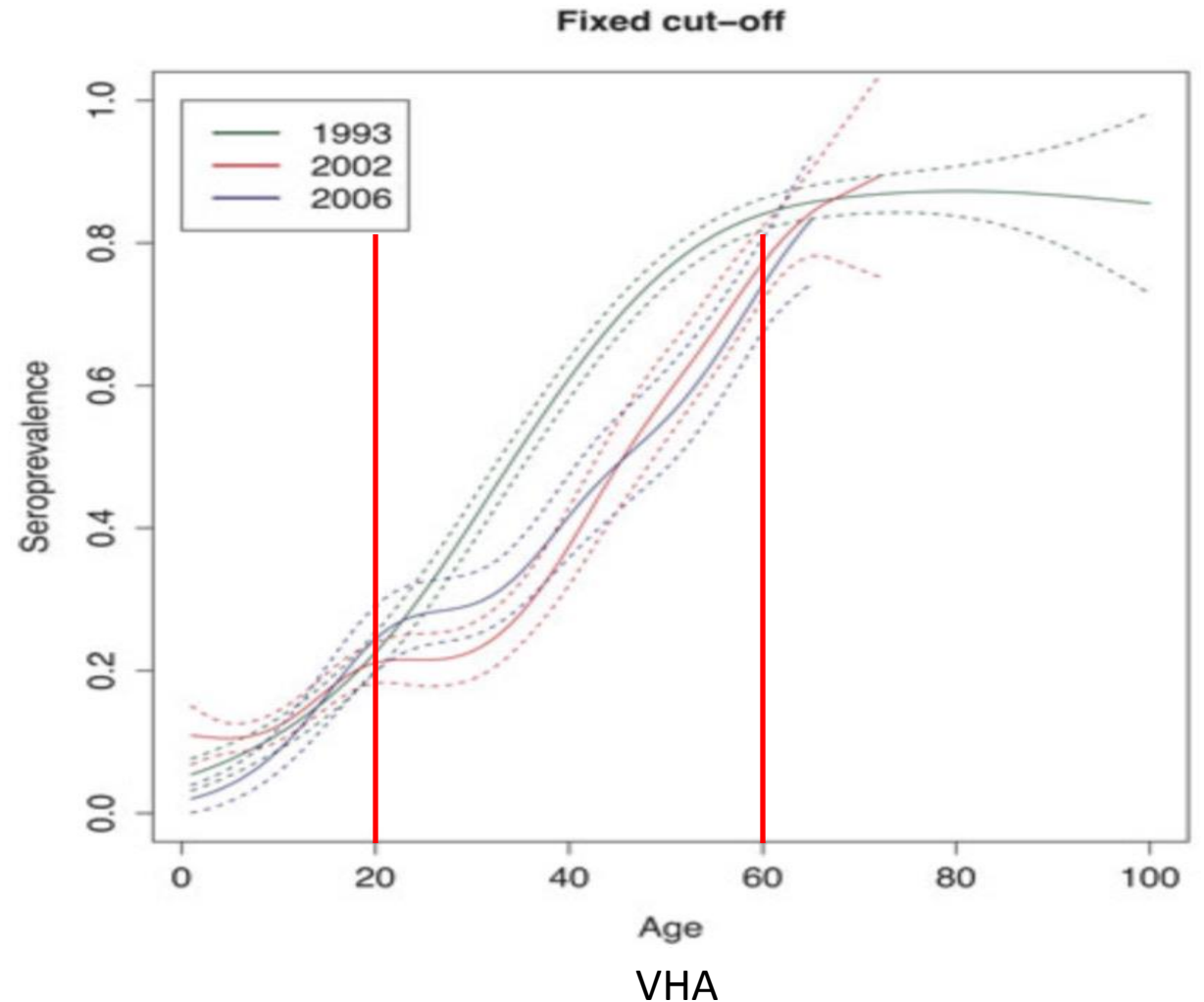
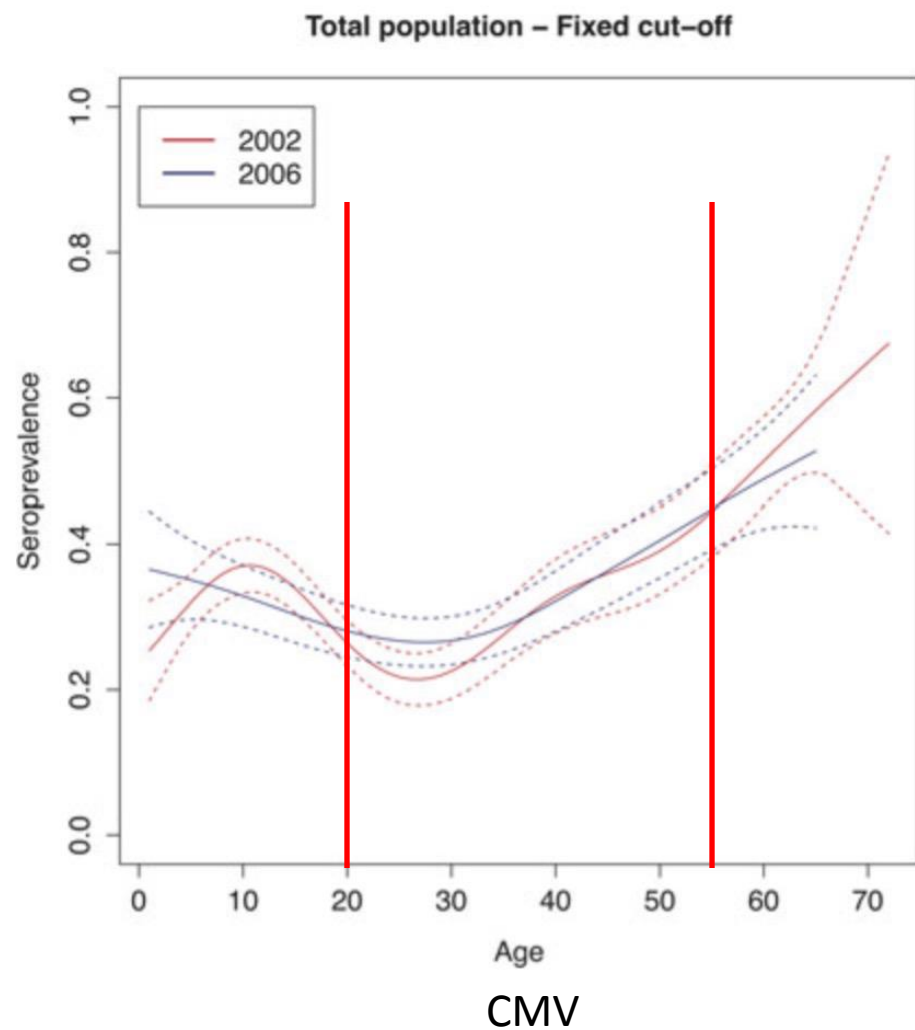
Europe et Canada



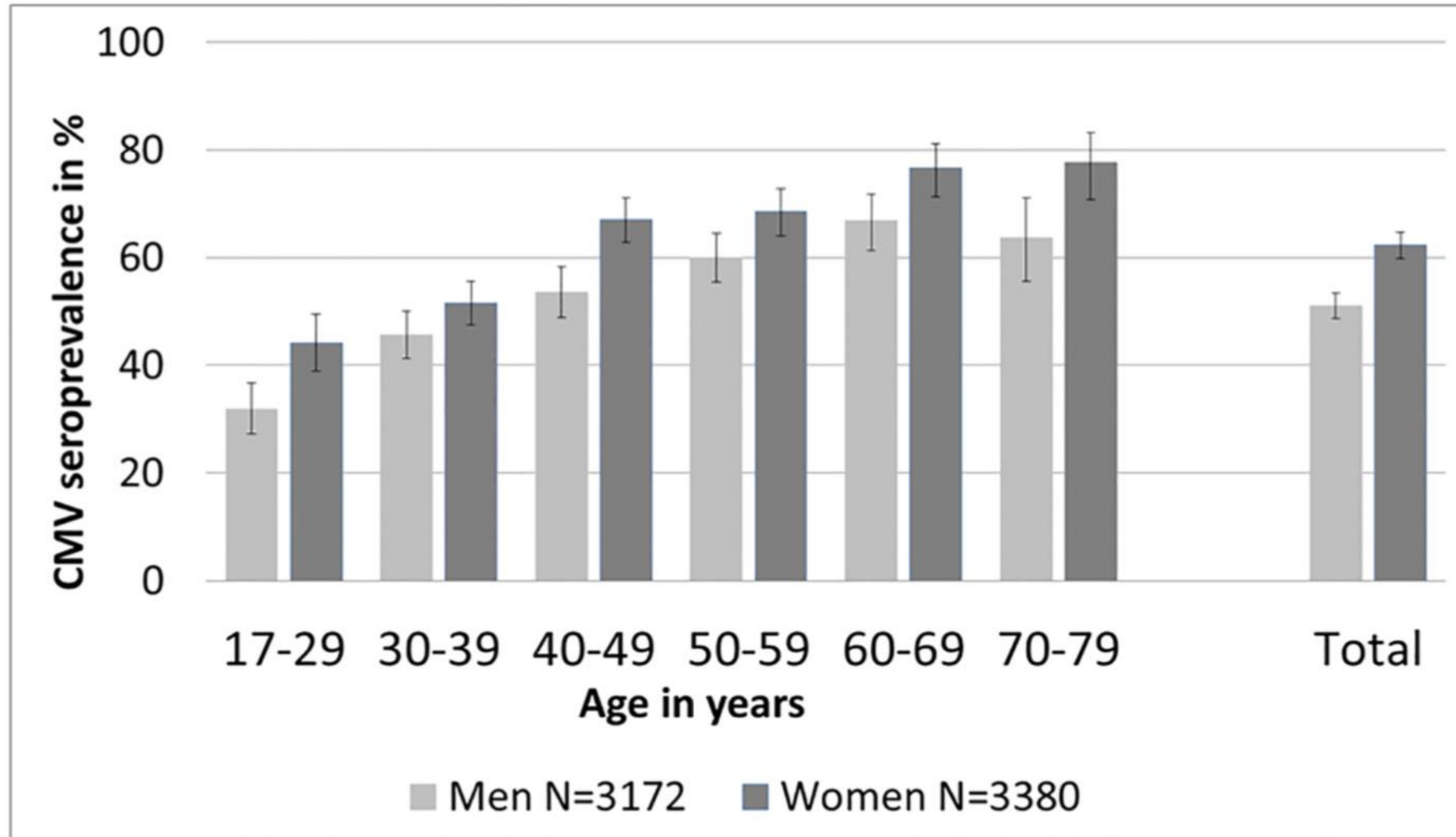
Epidémiologie: données récentes européennes :Belgique CMV vs VHA



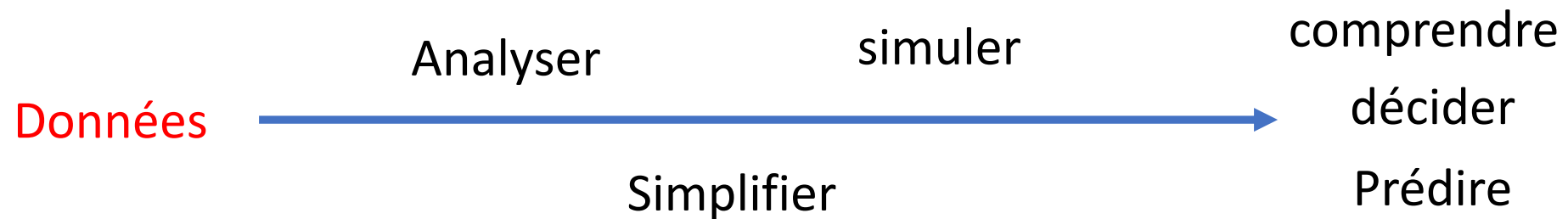
Epidémiologie: données récentes européennes : Belgique CMV vs VHA



Epidémiologie: données récentes européennes : Allemagne



Intérêt de la vaccination: Que disent les « modèles »?

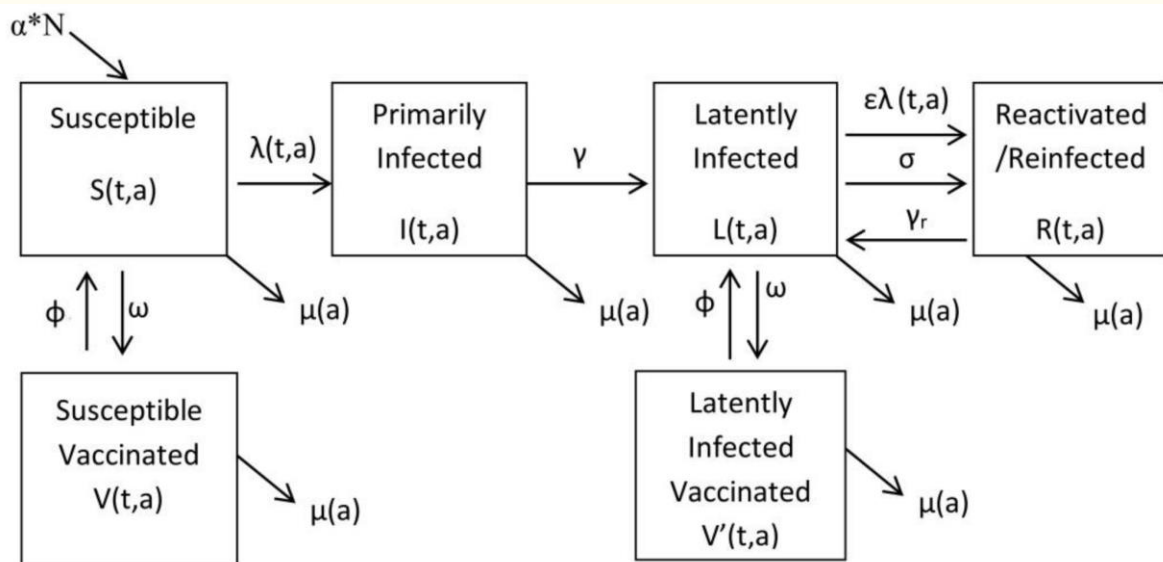


Efficacité de la vaccination

Table 1

Notation, definition and values of parameters in the mathematical model

| Notation | Definition | Value |
|--------------|--|---|
| $1/\gamma$ | Time to recover from primary infection | Age-specific: ≤ 5 year-olds: 2 years 6-19 year-olds: 1 year ≥ 20 year-olds: 0.5 year |
| $1/\gamma_r$ | Time to recover from non-primary infection | $(1/\gamma)/2$ |
| $1/\sigma$ | Time to reactivate CMV infection | 20 years or 5 years |
| ω | Effectively vaccinated proportion (vaccine coverage <i>times</i> vaccine efficacy) | 0-100% |
| $1/\phi$ | Time to lose vaccine protection | 2-50 years |



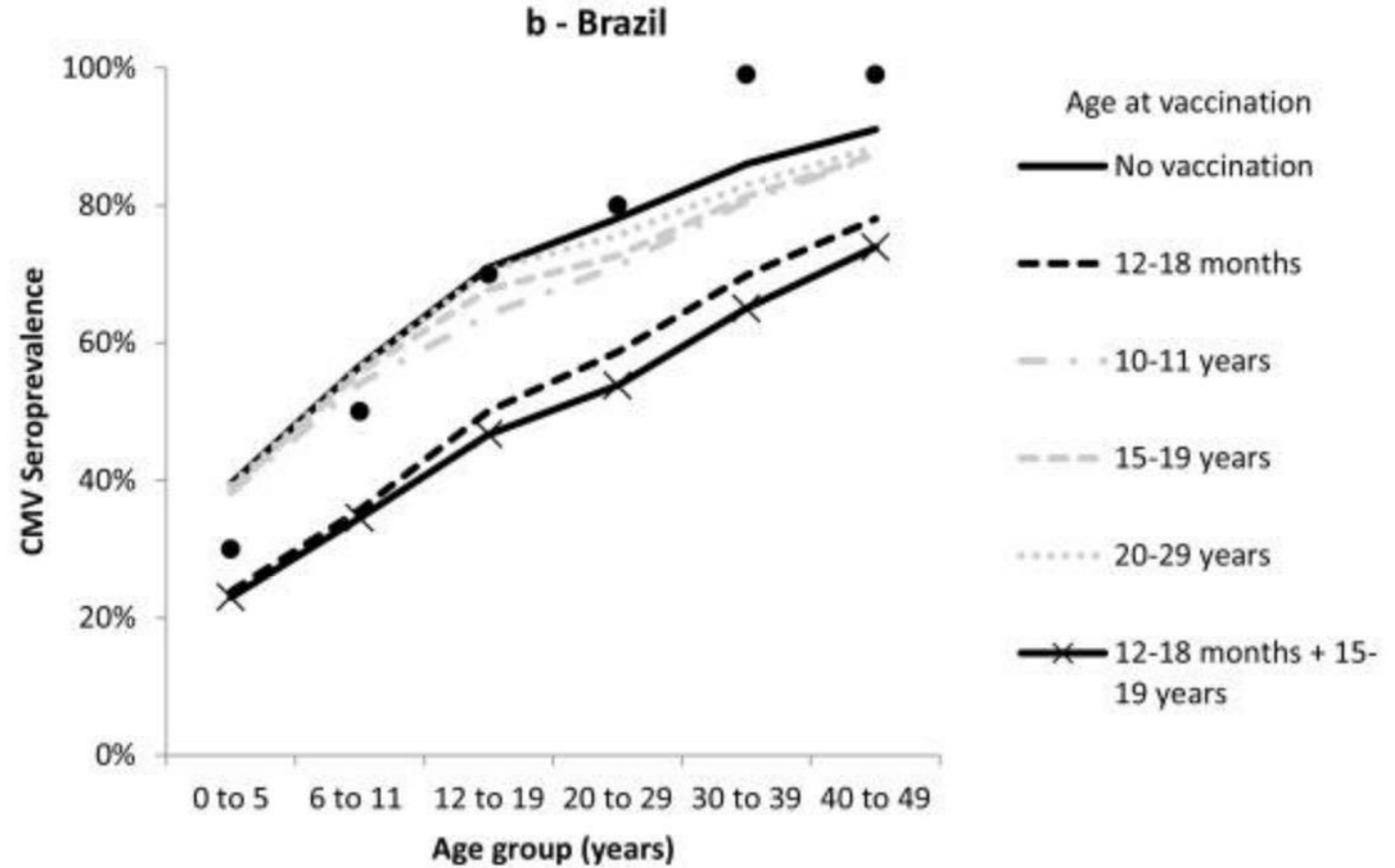
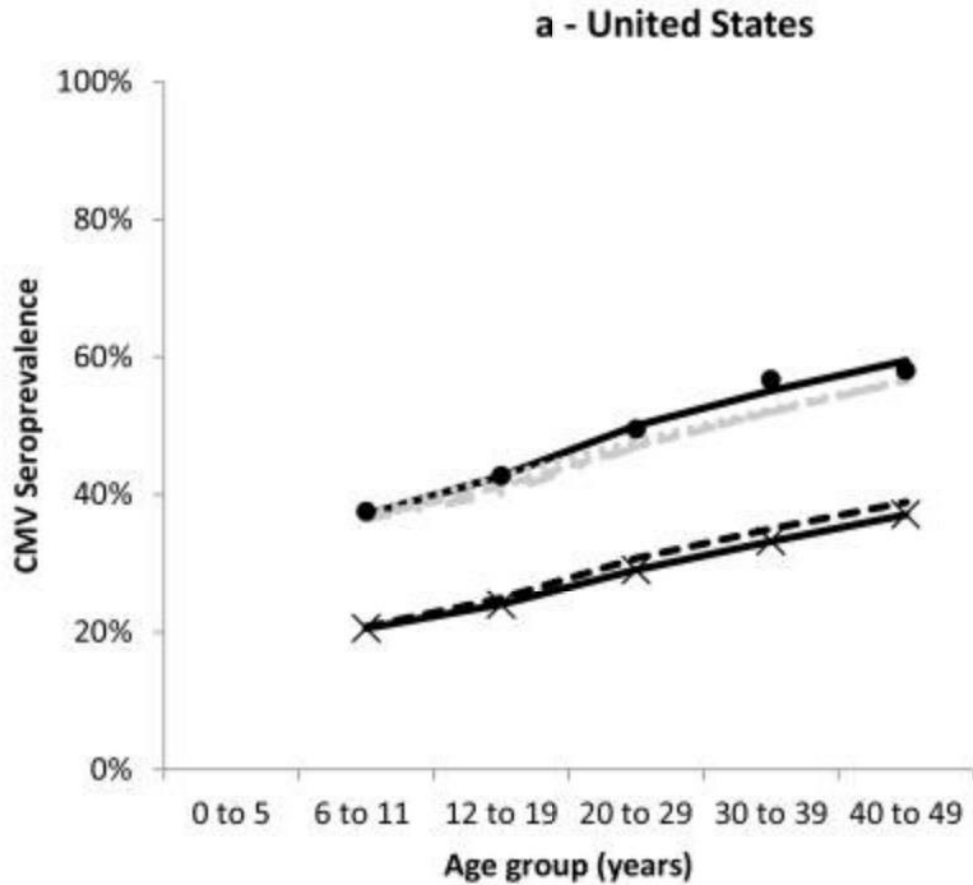
| Setting | Age at vaccination | Type of maternal infection | Distribution (%) of cCMV infections by type of maternal infection | | | | | | Reduction (%) in cCMV infections by type of maternal infection | | |
|---------------|--------------------|----------------------------|---|------------------------|----|----|------------------------|----|--|--|--|
| | | | Pre-Vaccination (Baseline) | Years Post-Vaccination | | | Years Post-Vaccination | | | | |
| | | | | 10 | 20 | 50 | 10 | 20 | 50 | | |
| | 12-18 months | Primary | 16 | 12 | 14 | 20 | 39 | 35 | 21 | | |
| | | Reinfection | 12 | 8 | 8 | 7 | 43 | 50 | 62 | | |
| | | Reactivation | 72 | 80 | 79 | 72 | 4 | 13 | 35 | | |
| | | Overall | 100 | | | | 14 | 21 | 36 | | |
| | | Overall | 100 | | | | 14 | 21 | 36 | | |
| | 15-19 years | Primary | 16 | 16 | 17 | 17 | 18 | 16 | 14 | | |
| | | Reinfection | 12 | 12 | 12 | 11 | 17 | 19 | 21 | | |
| | | Reactivation | 72 | 72 | 72 | 71 | 15 | 17 | 19 | | |
| | | Overall | 100 | | | | 16 | 17 | 18 | | |
| | | Overall | 100 | | | | 16 | 17 | 18 | | |
| United States | 12-18 months + | Primary | 16 | 11 | 14 | 22 | 49 | 44 | 29 | | |
| | | Reinfection | 12 | 8 | 7 | 7 | 53 | 58 | 69 | | |
| | | Reactivation | 72 | 81 | 79 | 72 | 17 | 25 | 45 | | |
| | | Overall | 100 | | | | 27 | 32 | 45 | | |
| | | Overall | 100 | | | | 27 | 32 | 45 | | |
| | 20-29 years | Primary | 16 | 18 | 18 | 18 | 27 | 24 | 23 | | |
| | | Reinfection | 12 | 12 | 12 | 12 | 32 | 32 | 32 | | |

Table 1

Notation, definition and values of parameters in the mathematical model

Reduction (%) in cCMV

Distribution (%) of cCMV infections by type of maternal infection



20-29 Remrection 12 12 12 12 32 32 32

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Notation, definition and values of parameters in the mathematical model

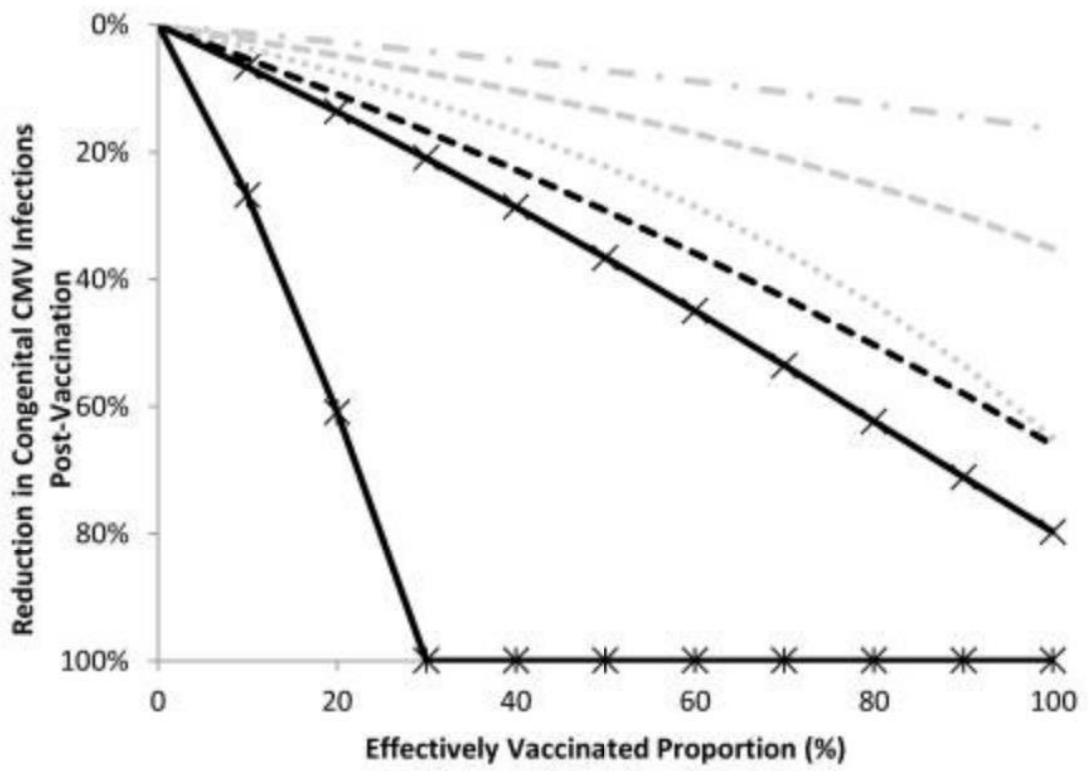
| Notation | Definition | Value |
|------------|--|---------------|
| $1/\gamma$ | Time to recover from primary infection | Age-specific: |

Distribution (%) of cCMV infections by type of maternal infection

Reduction (%) in cCMV infections by type of maternal infection

| Age at vaccination | Type of maternal infection | Pre-Vaccination | Years Post-Vaccination | | |
|----------------------------|----------------------------|-----------------|------------------------|----|----|
| | | (%) | 10 | 20 | 50 |
| 0-12 months | 10-11 years | 100 | 95 | 85 | 75 |
| 0-12 months | 15-19 years | 100 | 90 | 80 | 70 |
| 0-12 months | 20-29 years | 100 | 85 | 75 | 65 |
| 12-18 months | 10-11 years | 100 | 95 | 85 | 75 |
| 12-18 months | 15-19 years | 100 | 90 | 80 | 70 |
| 12-18 months | 20-29 years | 100 | 85 | 75 | 65 |
| 12-18 months + 15-19 years | 10-11 years | 100 | 95 | 85 | 75 |
| 12-18 months + 15-19 years | 15-19 years | 100 | 90 | 80 | 70 |
| 12-18 months + 15-19 years | 20-29 years | 100 | 85 | 75 | 65 |

a - United States



b - Brazil

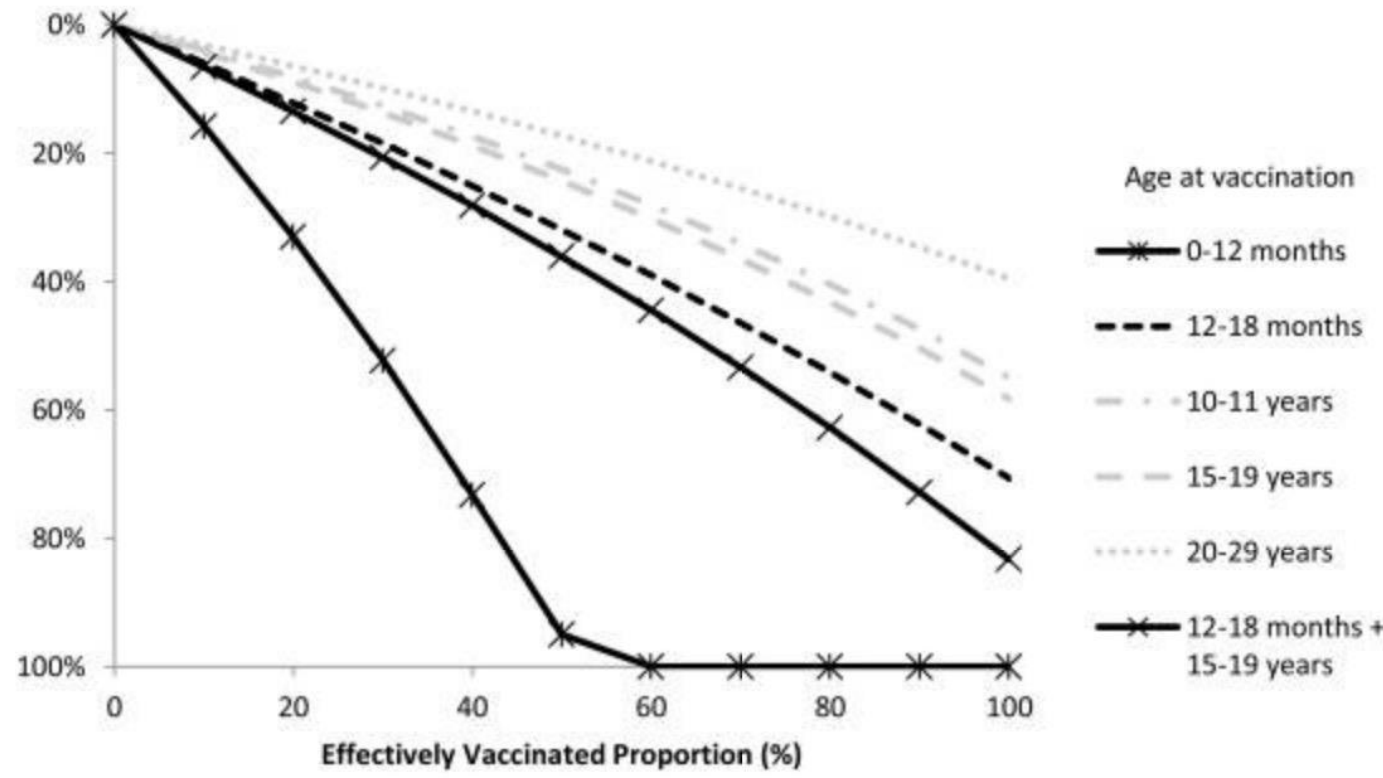
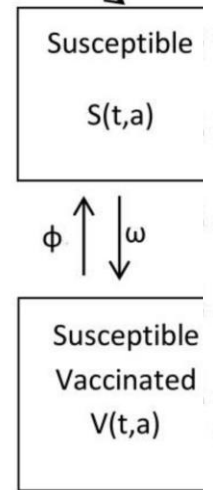


Table 1

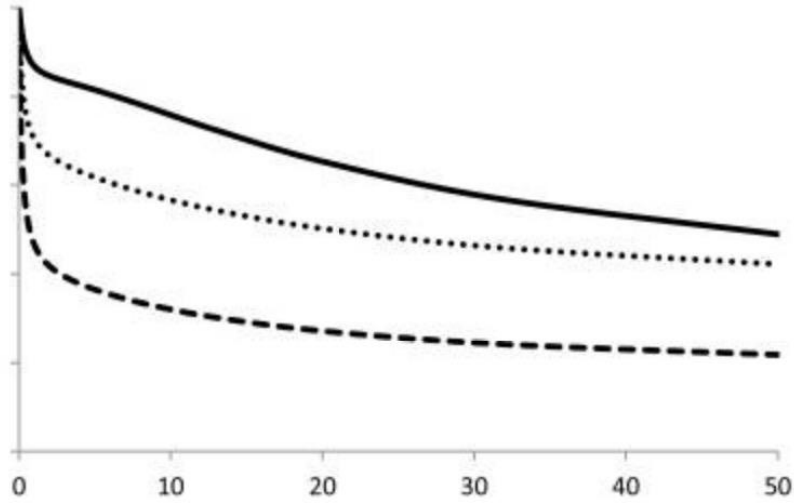
Notation, definition

| Notation | Definition |
|--------------|-----------------|
| $1/\gamma$ | Time |
| $1/\gamma_r$ | Time |
| $1/\sigma$ | Time |
| ω | Effective times |
| $1/\phi$ | Time |

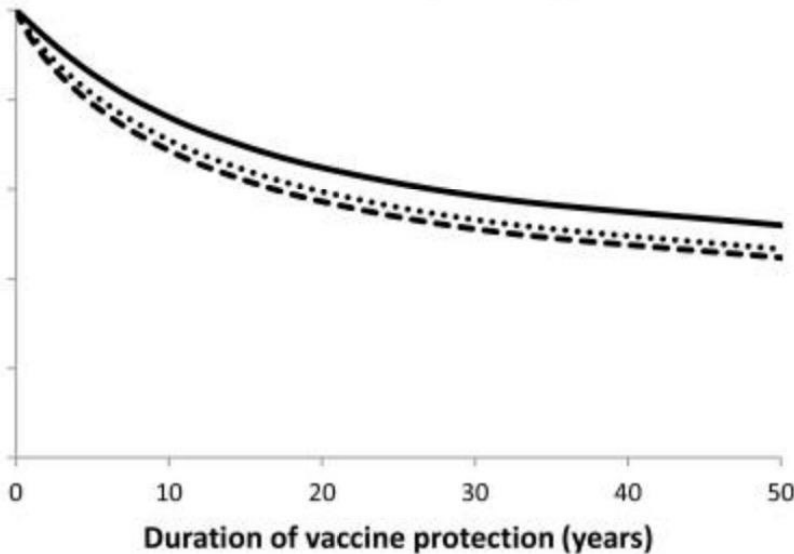
$\alpha * N$



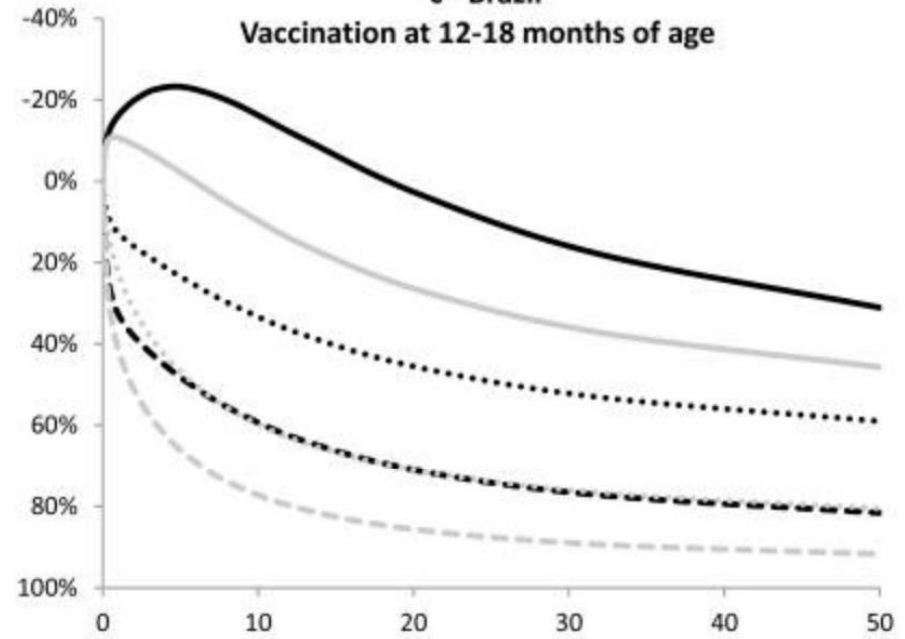
a - United States
Vaccination at 12-18 months of age



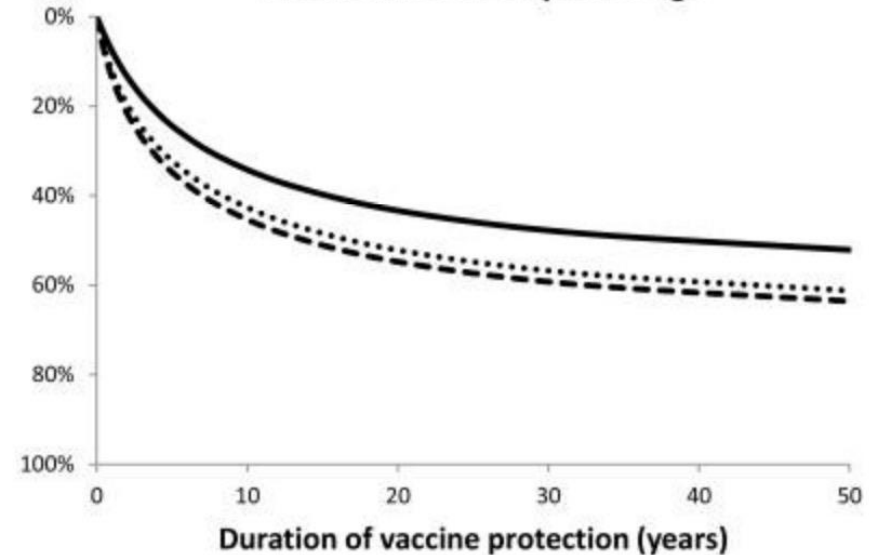
b - United States
Vaccination at 15-19 years of age



c - Brazil
Vaccination at 12-18 months of age



d - Brazil
Vaccination at 15-19 years of age



Infection (%) in cCMV infections by type of maternal infection

Years Post-Vaccination

| | 20 | 50 |
|--|----|----|
| | 35 | 21 |
| | 50 | 62 |
| | 13 | 35 |
| | 21 | 36 |
| | 16 | 14 |
| | 19 | 21 |
| | 17 | 19 |
| | 17 | 18 |
| | 44 | 29 |
| | 58 | 69 |
| | 25 | 45 |
| | 32 | 45 |
| | 24 | 23 |
| | 32 | 32 |

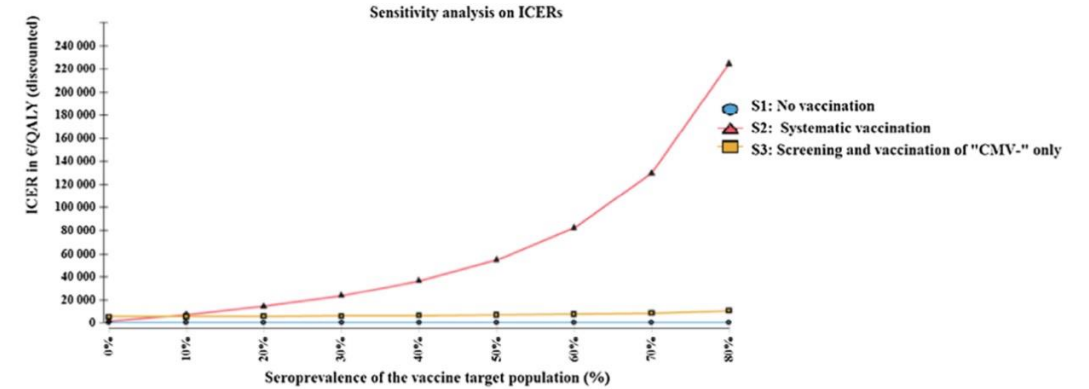
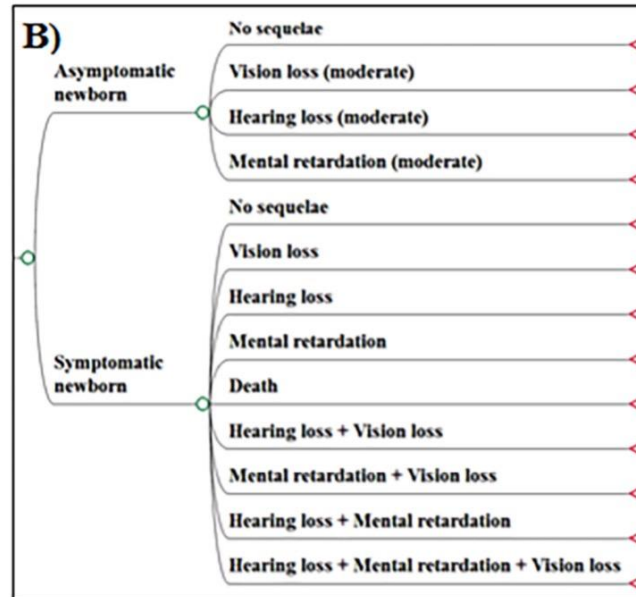
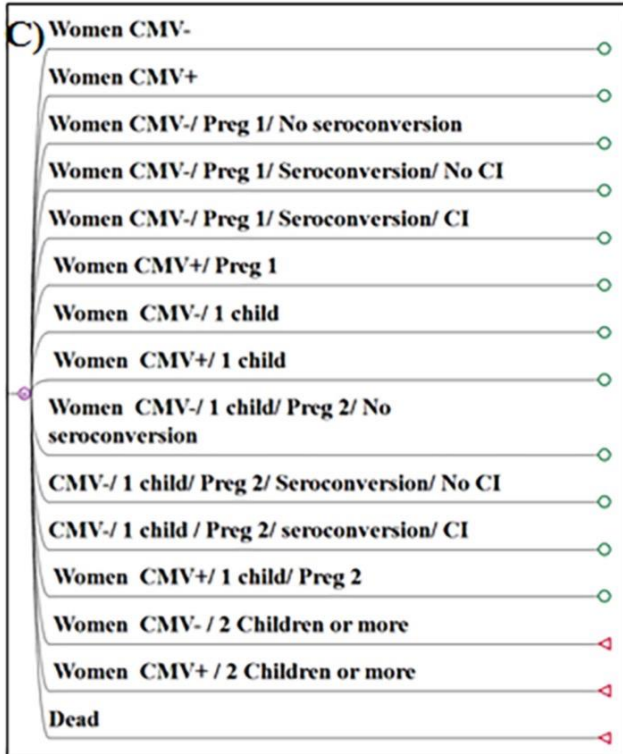
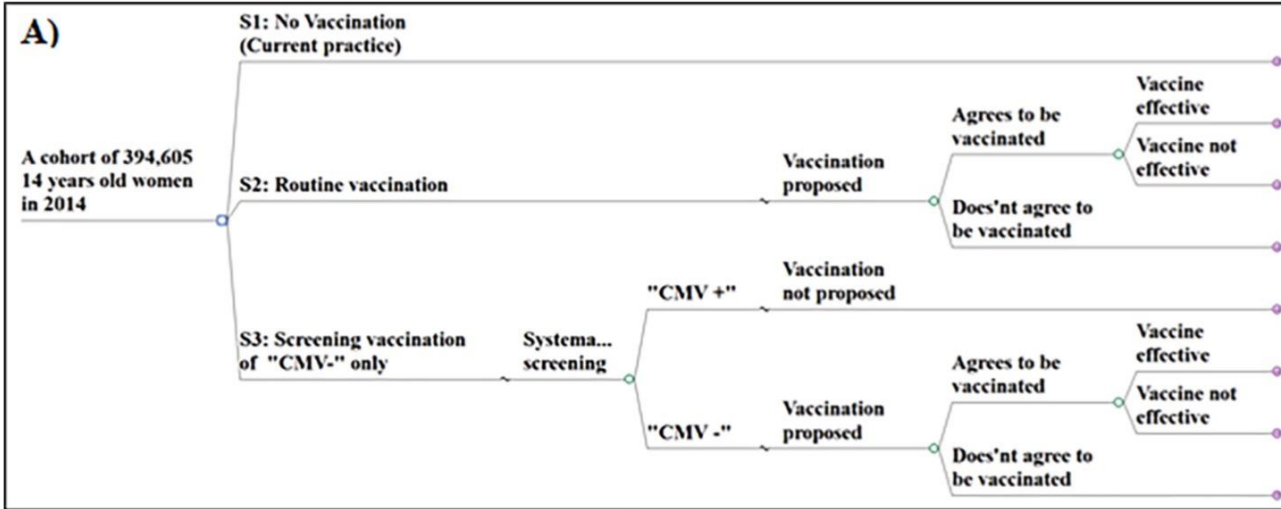


Fig. 2. One-way sensitivity analysis on the impact of CMV seroprevalence of the vaccine target population on incremental cost-effectiveness ratios. S: strategy; CMV-: women seronegative for cytomegalovirus; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

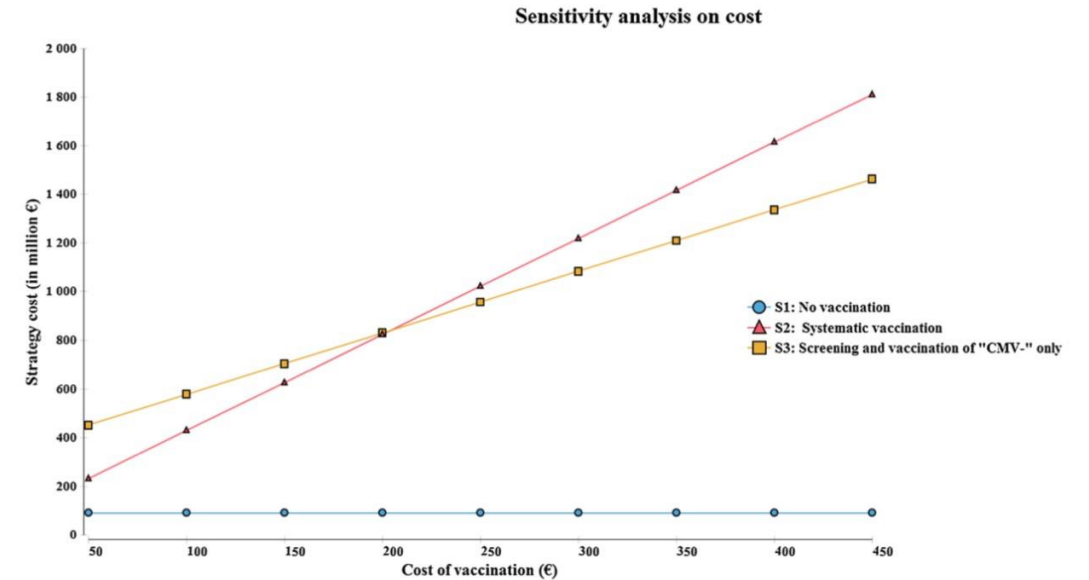


Fig. 3. One-way sensitivity analysis on the impact of vaccination cost on strategies global costs. S: strategy; CMV-: women seronegative for cytomegalovirus.

Faut-il un vaccin anti-CMV: Probablement mais:

- Cahier des charges ambitieux:
 - Protections contre plusieurs sérotypes (réinfections)
 - Expansion T8 similaire à l'immunité naturelle (réinfections, réactivations)
- Définition des cibles complexes:
 - Que les femmes?
 - Les femmes séronégatives ET séropositives?
 - Dès l'enfance?
- Impact économique à évaluer:
 - De la vaccination
 - De l'infection à CMV chez l'immunocompétent

| Row | Saved | Status | Study Title | Conditions | Interventions | Locations |
|-----|--------------------------|--|---|--|---|---|
| 1 | <input type="checkbox"/> | Completed | Trial of pDNA CMV Vaccine (VCL-CT02) Followed by Towne CMV Vaccine (Towne) Challenge | <ul style="list-style-type: none"> • Cytomegalovirus Infection | <ul style="list-style-type: none"> • Biological: VCL CT02 pDNA vaccine • Biological: Towne CMV vaccine | <ul style="list-style-type: none"> • UCSF Positive Health Program, 995 Potrero, 4th Floor San Francisco, California, United States |
| 2 | <input type="checkbox"/> | Recruiting | A Study of CMV Vaccine (HB-101) in Kidney Transplant Patients | <ul style="list-style-type: none"> • Cytomegalovirus (CMV) Infection • Kidney Transplantation | <ul style="list-style-type: none"> • Biological: HB-101 vaccine • Biological: placebo | <ul style="list-style-type: none"> • California Institute of Renal Research La Mesa, California, United States • California Pacific Medical Center San Francisco, California, United States • University of Colorado Hospital Aurora, Colorado, United States • (and 14 more...) |
| 3 | <input type="checkbox"/> | Completed | Study to Evaluate Safety and Immunogenicity of the GSK Bio CMV Vaccine in CMV-seronegative Healthy Male Adult Subjects | <ul style="list-style-type: none"> • Infections, Cytomegalovirus | <ul style="list-style-type: none"> • Biological: GSK Biologicals' Recombinant CMV gB Vaccine GSK1492903A | <ul style="list-style-type: none"> • GSK Investigational Site La Louvière, Belgium • GSK Investigational Site Wilrijk, Belgium |
| 4 | <input type="checkbox"/> | Completed Has Results | Evaluation of the Long-term Persistence of GlaxoSmithKline (GSK) Biologicals' Candidate Cytomegalovirus (CMV) Vaccine | <ul style="list-style-type: none"> • Infections, Cytomegalovirus | <ul style="list-style-type: none"> • Procedure: Blood sampling • Biological: GSK149203A | <ul style="list-style-type: none"> • GSK Investigational Site La Louvière, Belgium • GSK Investigational Site Wilrijk, Belgium |
| 5 | <input type="checkbox"/> | Completed | Recombinant CMV gB Vaccine in Postpartum Women | <ul style="list-style-type: none"> • Cytomegalovirus Infections | <ul style="list-style-type: none"> • Biological: CMV gB vaccine • Drug: MF59 adjuvant • Drug: Placebo | <ul style="list-style-type: none"> • University of Alabama at Birmingham Birmingham, Alabama, United States • University of Alabama at Tuscaloosa Tuscaloosa, Alabama, United States |
| 6 | <input type="checkbox"/> | Not yet recruiting | Cytomegalovirus (CMV) Vaccines: Reinfection and Antigenic Variation | <ul style="list-style-type: none"> • Cmv Congenital • CMV Viremia | <ul style="list-style-type: none"> • Diagnostic Test: Women Enrolled • Diagnostic Test: Newborns of Female Study Participants | <ul style="list-style-type: none"> • University of Sao Paulo São Paulo, Brazil |
| 7 | <input type="checkbox"/> | Unknown [†] | CMV Glycoprotein B Vaccine in Allograft Recipients | <ul style="list-style-type: none"> • Cytomegalovirus Infections | <ul style="list-style-type: none"> • Biological: CMV gB vaccine • Drug: Placebo | <ul style="list-style-type: none"> • University College Medical School London, United Kingdom |
| 8 | <input type="checkbox"/> | Completed | Phase 1 Trial of CMV Towne Vaccine in Subjects Previously Received VCL CT02 Vaccine ID or IM | <ul style="list-style-type: none"> • Cytomegalovirus Infection | <ul style="list-style-type: none"> • Biological: Towne CMV vaccine | |
| 9 | <input type="checkbox"/> | Active, not recruiting | A Study to Evaluate the Efficacy and Safety of a Vaccine, ASP0113, in Cytomegalovirus (CMV)-Seronegative Kidney Transplant Recipients Receiving an Organ From a CMV-Seropositive Donor | <ul style="list-style-type: none"> • Kidney Transplantation Cytomegalovirus (CMV) Negative Recipients | <ul style="list-style-type: none"> • Biological: ASP0113 • Drug: Placebo | <ul style="list-style-type: none"> • Site US10026 Phoenix, Arizona, United States • Site US10003 Los Angeles, California, United States • Site US10004 San Diego, California, United States • (and 50 more...) |
| 10 | <input type="checkbox"/> | Completed | gB/MF59 Vaccine in Preventing Cytomegalovirus Infection in Healthy Adolescent Females | <ul style="list-style-type: none"> • Cytomegalovirus Infections | <ul style="list-style-type: none"> • Biological: MF-59 • Drug: Placebo • Biological: CMV gB vaccine | <ul style="list-style-type: none"> • Cincinnati Children's Hospital Medical Center - Infectious Diseases Cincinnati, Ohio, United States • Vanderbilt University - Pediatric - Vanderbilt Vaccine Research Center Nashville, Tennessee, United States • The University of Texas Medical Branch - Sealy Center for Vaccine Development (SCVD) |

Merci