The Role of Mathematical Models in Vaccine Evaluation

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Claudio José Struchiner[1]

[1]Programa de Computação Científica
Fundação Oswaldo Cruz
stru@fiocruz.br

Instituto de Medicina Social
UERJ

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Epidemiological Reasoning

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Figure: Exposure definition, outcome definition, link function, sources of uncetainties

Realism, Generality, Precision: Legitimate vs Illegitimate Simplifications

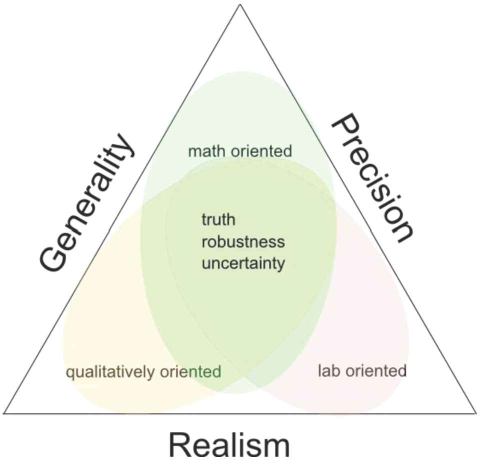


Figure: Paradigm “tension”

Useful quotes

Far better an approximate answer to the right question, which is often vague, than an exact answer to the wrong question, which can always be made precise (John W. Tukey).

No matter how beautiful your theory, no matter how clever you are or what your name is, if it disagrees with experiment, it's wrong (Richard Feynman).

Entities should not be multiplied beyond necessity (Occam's Razor)

Parameters of interest

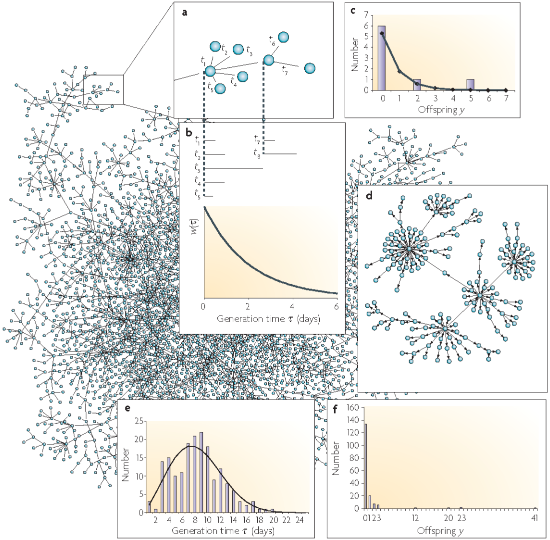


Figure: Basic parameters (Grassly 2008)

R_0 as a threshold parameter

$$
\begin{aligned}
R_0 &< 1 \\
p_c &= \frac{R_0 - 1}{R_0} = 1 - \frac{1}{R_0}
\end{aligned}
$$

Epidemiological Reasoning

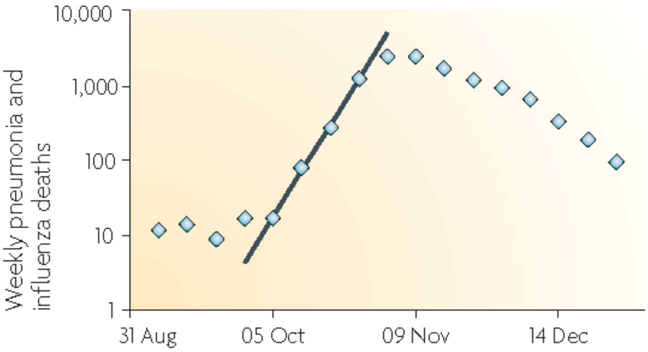


Figure: Estimating R_0 (Grassly 2008)

Malaria Life Cycle

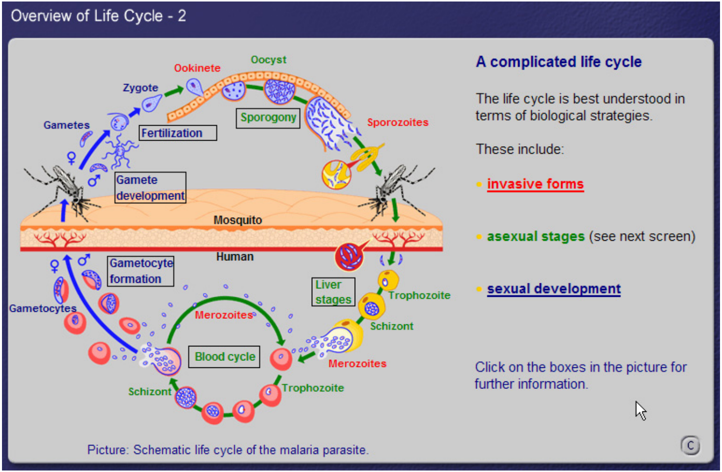


Figure: Example: biology of malaria

Epidemiological Translation of the life cycle: epidemiological categories

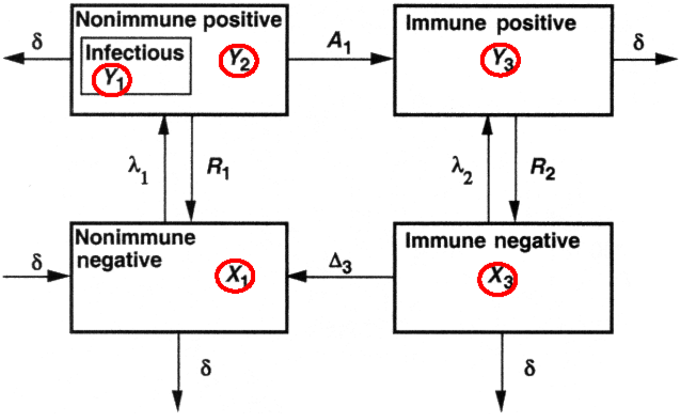


Figure: Morbidity, immunity, and degree of infectiousness (super-spreader), distribution clusters

Epidemiological Translation of the life cycle: incidence rates

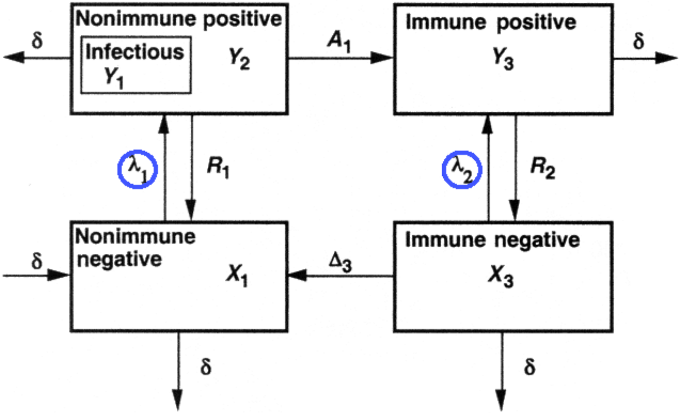


Figure: Dependence on the number of previously infected, vector density, vector competence, superinfection, within host competition, bottlenecks, incomplete immunity.

Epidemiological Translation of the life cycle: recovery rates

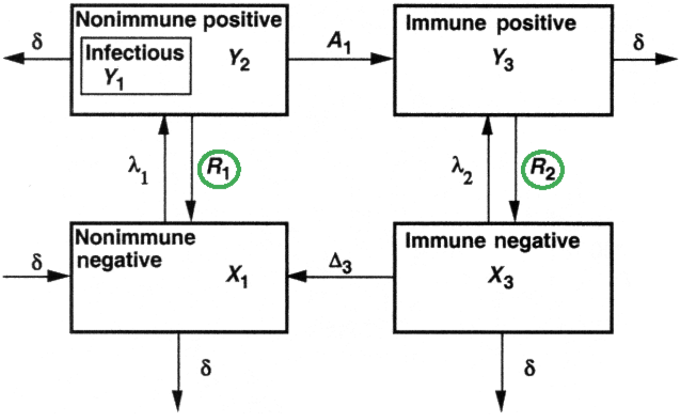


Figure: Dependence on parasite load, immune memory, superinfection, within host competition, bottlenecks.

Epidemiological Translation of the life cycle: rates of acquisition and loss of immunity

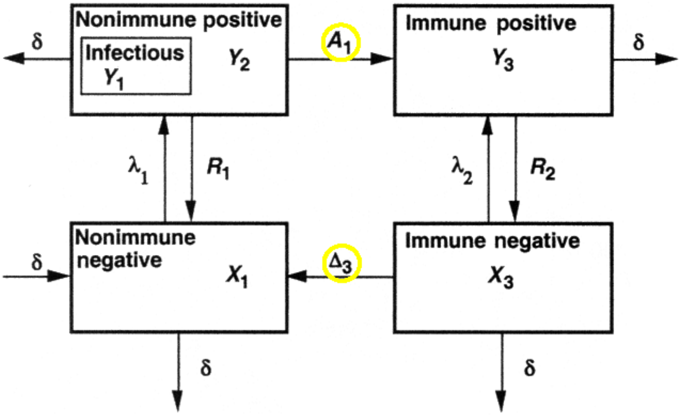


Figure: Phenomena in various levels, time delays, immune boosting.

Epidemiological Translation of the life cycle: demographic rates

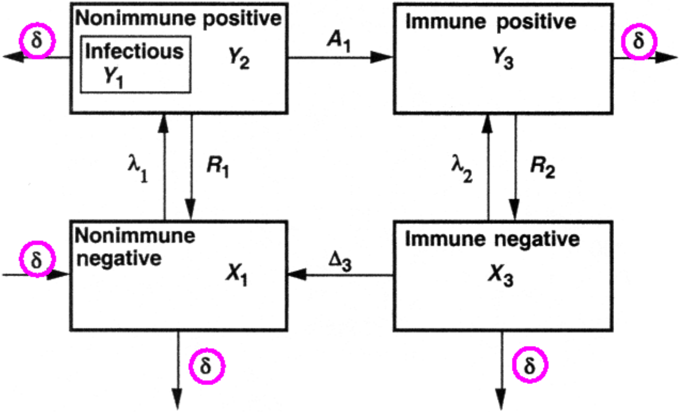


Figure: Migration, seasonality, age structure.

Mechanisms of action and intervention delivery

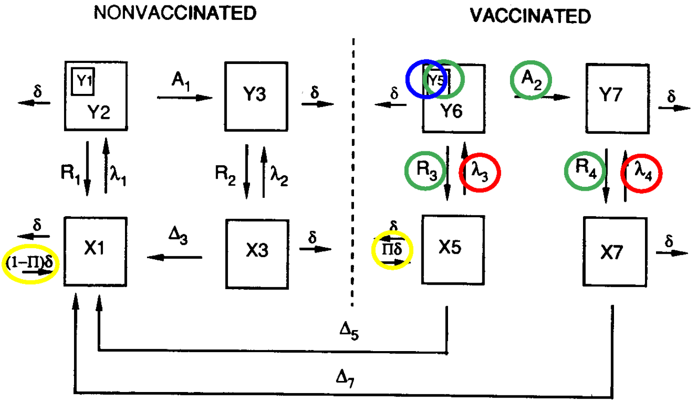


Figure: Infection blocking, disease modifying, and transmission blocking; pulse, continuous, campaign

Model Equations

$$\begin{aligned}
\frac{\partial x_1}{\partial t} &= \delta + R_1(r_1, z_1, z_2)y_2 - (\lambda_1 + \delta)x_1 + \Delta_3(t) \\
\frac{\partial x_3}{\partial t} &= R_2(r_2, z_3)y_3 - (\lambda_2 + \delta)x_3 - \Delta_3(t) \\
\frac{\partial y_2}{\partial t} &= \lambda_1 x_1 - [A_1(\alpha_2, z_1, z_2) + R_1(r_1, z_1, z_2) + \delta]\, y_2 \\
\frac{\partial y_3}{\partial t} &= \lambda_2 x_3 + A_1(\alpha_2, z_1, z_2)y_2 - [R_2(r_2, z_3) + \delta]\, y_3 \\
y_1 &= \frac{1 - e^{-z_1}}{1 - e^{-(z_1+z_2)}} y_2, \quad \lambda_i = m_3(t - N_1)ab_i \\
\frac{\partial z_1}{\partial t} &= \lambda_1 - \alpha_1 z_1, \quad \frac{\partial z_2}{\partial t} = \alpha_1 z_1 - r_1 z_2, \quad \frac{\partial z_3}{\partial t} = \lambda_2 - r_2 z_3 \\
R_1 &= r_1 z_2 \frac{e^{-(z_1+z_2)}}{1 - e^{-(z_1+z_2)}}, \quad R_2 = r_2 z_3 \frac{e^{-z_3}}{1 - e^{-z_3}} \\
A_1(\alpha_2, z_1, z_2) &= \alpha_2 \left(1 - e^{-(z_1 + z2)}\right) \\
\Delta_3(t) &= \Big\{ R_2(r_2, z_3, t - \tau)y_3(t - \tau) + (f - b_2)h_e(t - \tau) \\
&\quad \left[x_3(t - \tau) - b_2 \int_{t-\tau-N_1}^{t-\tau} h_e(u)x_3(u)du \right] \Big\} e^{-(\bar{h}_b + \delta)\tau} \\
\bar{h}_b &= \int_{t-\tau}^{t} \frac{h_b(u)}{\tau} du, \quad h_b(t) = m_3(t)af, \quad b_2 \le f \le 1
\end{aligned}$$

[?]

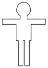
Glossary

- A_1 rate at which immunity to *P. falciparum* infection is acquired by a human host
- b_1 prop. of bites by infec. mosquitoes on neg. nonimmune hosts actually resulting in infec.
- b_2 prop. of bites by infectious mosquitoes on neg. immune hosts actually resulting in infec.
- f boosting factor (prop. of bites by infec. mosq. on immune hosts that boost immunity)
- h_e entomologic inoc. rate (EIR): # of P. falciparum infectious bites per human per day
- N_1 *P. falciparum* parasitemia incubation period in humans (in days)
- r_1 rate ctt of elimination of a brood of parasites by nonimmune positive hosts (in days^{-1})
- r_2 rate constant of elimination of a brood of parasites by immune positive hosts (in days^{-1})
- R_1 recovery rate for nonimmune positive individuals (in days^{-1})
- R_2 recovery rate for immune positive individuals (in days^{-1})
- X_1 proportion of nonimmune negative (i.e., naive) individuals in the population
- X_3 proportion of immune negative individuals
- Y_1 proportion of nonimmune positive individuals potentially infectious for mosquitoes
- Y_2 proportion of nonimmune positive individuals
- Y_3 proportion of immune positive individuals
- z_1 average number of infectious broods of the parasite per nonimmune positive human host
- z_2 average number of noninfectious broods of the parasite per nonimmune positive human host
- z_3 average number of noninfectious broods of the parasite per immune positive human host
- α_1 recovery rate from infectiousness to mosquitoes among nonimmune positive hosts (in days^{-1})
- α_2 maximum rate at which immunity to P. falciparum infection can be acquired (in days^{-1})
- δ death and birth rate in the human population (in days^{-1})
- Δ_3 daily fraction of immune negative subjects losing immunity
- λ_1 infection rate for nonimmune negative subjects (probability per day of such a subject's becoming infected)
- λ_2 infection rate for immune negative subjects (probability per day of such a subject's becoming infected)
- τ time delay needed for an immune host to lose immunity in the absence of exposure to infection (in days)

Measure of intervention efficacy

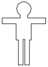
<u>In the lab:</u>

\# of cases



V, E, PE
KC, UC

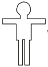
\# of cases



NV, E,PE
KC, UC

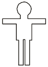
<u>In the field:</u>

\# of cases



V, E?, PE?
KC, UC

\# of cases



NV, E?, PE?
KC, UC

V, NV - treatment (vaccination)
E, PE - transmission level, previous exp
KC, UC - known and unknown covaritates

Challenge: Exposure to infection

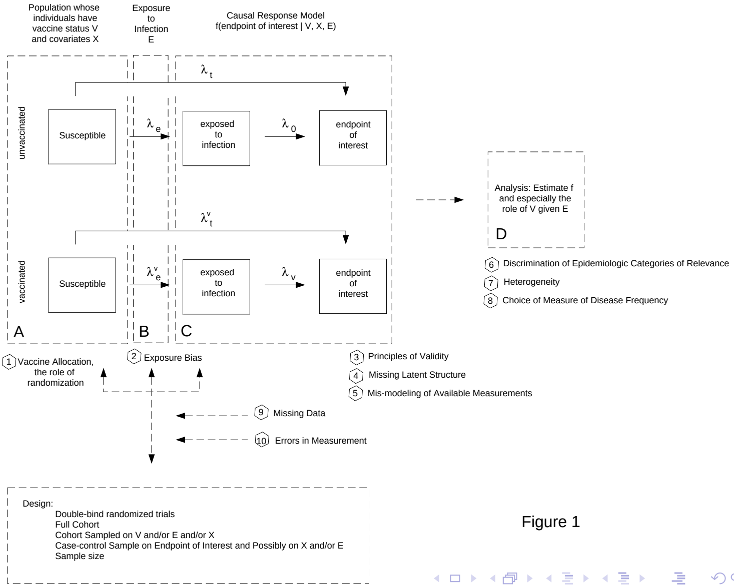


Figure 1

Study designs for dependent happenings

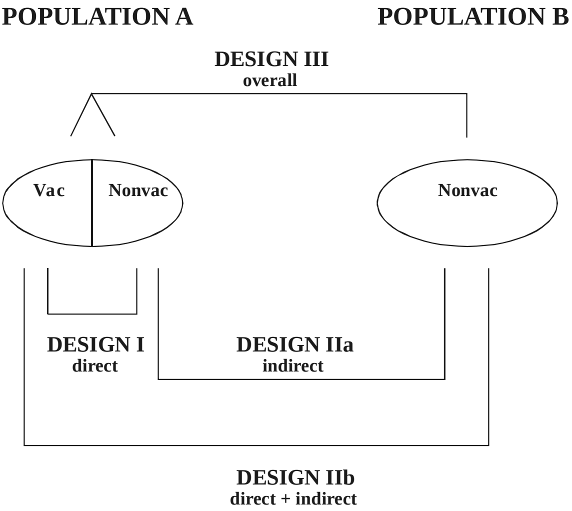


Figure: Direct, indirect and overall effects

Behavior of common measures of intervention efficacy

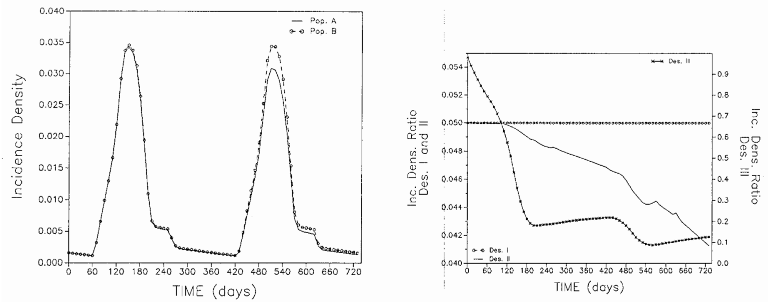


FIGURE 1a *Incidence (effective inoculation rate) in non-immune susceptibles of populations A and B during the first two years of observation.*

FIGURE 1b *Incidence density ratio calculated for the same simulation as in Figure 1.*

Figure: The behavior of common measures of association under a complex disease transmission pattern.

Hierarchical interpretation of common measures of efficacy

TABLE 1. Parameters used for measuring various effects of vaccination*

Level	Parameter choice	Comparison groups and effect: Susceptibility	Infectiousness	Combined change in susceptibility and infectiousness	
	Conditional on exposure to infection:				
I	Transmission probability, p Secondary attack rate (SAR)	$VE_{S,p}\dagger = 1 - \frac{p_{01}}{p_{00}}$	$VE_{I,p} = 1 - \frac{p_{10}}{p_{00}}$	$VE_{T,p} = 1 - \frac{p_{11}}{p_{00}}$	
		Study design			
		I direct	IIA indirect	IIB total	III overall
	Unconditional:				
II	Incidence rate (IR)	$VE_{S,IR} = 1 - \frac{IR_{A1}}{IR_{A0}}$	$VE_{IIA,IR} = 1 - \frac{IR_{A0}}{IR_{B0}}$	$VE_{IIB,IR} = 1 - \frac{IR_{A1}}{IR_{B0}}$	$VE_{III,IR} = 1 - \frac{f IR_{A1} + (1-f) IR_{A0}}{IR_{B0}}$
	Hazard, λ	$VE_{S,\lambda} = 1 - \frac{\lambda_{A1}}{\lambda_{A0}}$	$VE_{IIA,\lambda} = 1 - \frac{\lambda_{A0}}{\lambda_{B0}}$	$VE_{IIB,\lambda} = 1 - \frac{\lambda_{A1}}{\lambda_{B0}}$	$VE_{III,\lambda} = 1 - \frac{f\lambda_{A1} + (1-f)\lambda_{A0}}{\lambda_{B0}}$
III	Proportional hazards (PH)	$VE_{S,PH} = 1 - e^{\beta_1}$	NA†	NA	NA
IV	Cumulative incidence (CI)	$VE_{S,CI} = 1 - \frac{CI_{A1}}{CI_{A0}}$	$VE_{IIA,CI} = 1 - \frac{CI_{A0}}{CI_{B0}}$	$VE_{IIB,CI} = 1 - \frac{CI_{A1}}{CI_{B0}}$	$VE_{III,CI} = 1 - \frac{f CI_{A1} + (1-f) CI_{A0}}{CI_{B0}}$

Figure: Interpretation of efficacy measures

EID

CJ Struchiner

Reasoning

Reasoning Infectious

Intervention

Mechanisms

Equations

Glossary

Biological efficacy

Challenge

Study Design

Behavior

Hierarchy

Causal inference

Causal inference for infectious diseases

All Non-vaccinated	All Vaccinated	Fraction Vaccinated = 2/6	Fraction Vaccinated = 2/6	Fraction Vaccinated = 3/6
$\mathrm{Tom}^{+}_{NV} \to \mathrm{Harry}^{+}_{NV}$, $\mathrm{Tom}^{+}_{NV} \to \mathrm{Sally}^{+}_{NV}$	$\mathrm{Tom}^{-}_{V} \to \mathrm{Harry}^{-}_{V}$, $\mathrm{Tom}^{-}_{V} \to \mathrm{Sally}^{-}_{V}$	$\mathrm{Tom}^{+}_{NV} \to \mathrm{Harry}^{+}_{NV}$, $\mathrm{Tom}^{+}_{NV} \to \mathrm{Sally}^{-}_{V}$	$\mathrm{Tom}^{-}_{V} \to \mathrm{Harry}^{-}_{NV}$, $\mathrm{Tom}^{-}_{V} \to \mathrm{Sally}^{-}_{NV}$	$\mathrm{Tom}^{-}_{V} \to \mathrm{Harry}^{-}_{NV}$, $\mathrm{Tom}^{-}_{V} \to \mathrm{Sally}^{-}_{V}$
$\mathrm{John}^{+}_{NV} \to \mathrm{Paul}^{+}_{NV}$, $\mathrm{John}^{+}_{NV} \to \mathrm{Mary}^{+}_{NV}$	$\mathrm{John}^{-}_{V} \to \mathrm{Paul}^{-}_{V}$, $\mathrm{John}^{-}_{V} \to \mathrm{Mary}^{-}_{V}$	$\mathrm{John}^{+}_{NV} \to \mathrm{Paul}^{+}_{NV}$, $\mathrm{John}^{+}_{NV} \to \mathrm{Mary}^{+}_{V}$	$\mathrm{John}^{-}_{V} \to \mathrm{Paul}^{-}_{NV}$, $\mathrm{John}^{-}_{V} \to \mathrm{Mary}^{-}_{NV}$	$\mathrm{John}^{+}_{NV} \to \mathrm{Paul}^{+}_{NV}$, $\mathrm{John}^{+}_{NV} \to \mathrm{Mary}^{+}_{V}$
$E(Y_0) = 1$	$E(Y_1) = 0$	$\frac{\Sigma (Y_{i0} \mid S_i = 0)}{N_0} = \frac{4}{4}$	$\frac{\Sigma (Y_{i0} \mid S_i = 0)}{N_0} = \frac{0}{4}$	$\frac{\Sigma (Y_{i0} \mid S_i = 0)}{N_0} = \frac{2}{3}$
		$\frac{\Sigma (Y_{i1} \mid S_i = 1)}{N_1} = \frac{1}{2}$	$\frac{\Sigma (Y_{i1} \mid S_i = 1)}{N_1} = \frac{0}{2}$	$\frac{\Sigma (Y_{i1} \mid S_i = 1)}{N_1} = \frac{1}{3}$
1 - 0 = 1		1 - 1/2 = 1/2	0 - 0 = 0	2/3 - 1/3 = 1/3