Mathematical model for control of measles by vaccination

Ousmane MOUSSA TESSA*
Department of Mathematics and Computer Science,
Abdou Moumouni University, Niamey, NIGER.

Abstract

Protecting children from vaccine-preventable diseases, such as measles, is among primary goals of health administrators worldwide. Since vaccination turned out to be the most effective strategy against childhood diseases, developing a framework that would predict an optimal vaccine coverage level needed to control the spread of these diseases is crucial. In this article, we use a compartmental mathematical model of the dynamics of measles spread within a population with variable size to provide this framework. We rely on a compartmental model expressed by a set of differential equations based on the dynamics of measles infection. In order to apply vaccination strategies, theoretical results show that adding a second opportunity strategy to the routine immunization program enhances herd immunity with lower vaccination coverage.

Keywords : Measles, compartmental mathematical model, herd immunity, second opportunity.

1 Introduction

The Measles virus is a paramyxovirus, genus Morbillivirus. Measles is an infectious disease highly contageneous through person-to-person transmission mode, with $> 90\%$ secondary attack rates among susceptible persons. It is the first and worst eruptive fever occuring during childhood. It produces also a characteristic red rash and can lead to serious and fatalcomplications including pneumonia, diarrhaea and encephalitis. Many infected children subsequently suffer blindness, deafness or impaired vision. Measles confer life long immunity from further attacks ([4]).

Worldwide, measles vaccination has been very effective, preventing an estimated 80 million cases and 4.5 million deaths annually [8]. Although global incidence has been significantly reduced through vaccination, measles remains an important public health problem. Since vaccination coverage is not uniformly high worldwide, measles stands as the leading vaccine-preventable killer of children worldwide; measles is estimated to have caused 614 000 global deaths annually in 2002, with more than half of measles deaths occur in sub-saharan Africa ([9],[7]).

The World Health Assembly in 1989 and the World Summit for Children in 1990 set goals for measles morbidity and mortality reduction of 90% and 95%, respectively, compared with prevaccine levels. Therefore, vaccination against measles with one dose is one of the components of WHO's EPI (World Health Organisation's Expanded Programme on Immunization) implemented from the 1980's in most sub-saharan Africa countries. The fondamental characteristic of vaccination is that it reduces the incidence of disease in those immunized, the susceptibles. Also, vaccination protects indirectly non-vaccinated susceptibles against infection by producing herd immunity.

Find threashold conditions that determine whether an infectious disease will spread or will die out into a population remains one of the fundamental questions of epidemiological modeling. For this purpose,

*E-mail: musatesa@yahoo.com

there exists a key epidemiological quantity R_0, the basic reproductive ratio. R_0 is the number of secondary cases that result from a single infectious individual in an entirely susceptible population. Introduced by Ross in 1909 ([1], the current usage of R_0 is the following : if $R_0 < 1$, the modeled disease dies out, and if $R_0 > 1$, the disease spreads in the population. Reproductive ratios turned out to be an important factor in determining targets for vaccination coverage. In mathematical models, the reproductive number R_0 is determined by the dominant eigenvalue of the Jacobian matrix at the infection-free equilibrium for models in a finite-dimensional space.

The paper is organized as follows : Section 2 introduces the formulation of model using study the dynamics of measles in the presence a vaccine. The reproductive numbers are computed in Section 3 and the qualitative behavior of the disease-free steady state is also studied. In Section 4, we apply our results to vaccination policies and study related optimal strategies. Section 5 is devoted to discussions about our results and next future work.

2 The model equations

Following the classical assumption ([1], [2], [3]), we formulate a deterministic, compartmental, mathematical model to describe the transmission dynamics of measles. The population is homogeneously mixing and reflects the demography of a typical developing country, as it experiments an exponential increasing dynamics.

Compartments with labels such as S, E, I, and R are often used for the epidemiological classes. As most mothers has been infected, IgG antibodies transferred across the placenta, to newborn infants give them temporary passive immunity to measles' infection ([4], [2]). After the maternal antibodies remains in the body up to nine months, we consider that the infant enters directly in the susceptible class S at birth. So, all the newborns were assumed to be susceptible. When there is an adequate contact of a susceptible with an infective so that transmission occurs, then the susceptible enters the exposed class E of those in the latent period, who are infected but not yet infectious. After the latent period ends, the individual enters the class I of infectives, who are infectious in the sense that they are capable of transmitting the infection. When the infectious period ends, the individual enters the recovered class R consisting of those with! permanent infection-acquired immunity, otherwise passes away. We exclude vertical incidence in our model, which means that the infection rate of newborns by their mothers. Our model belongs to a more general SEIR transmission model.

Vaccination is an effective way to control the transmission of measles. Interrupting horizontal transmission by appropriate immunization program is expected to have a signifiant impact on the rate of acquisition of new infected.

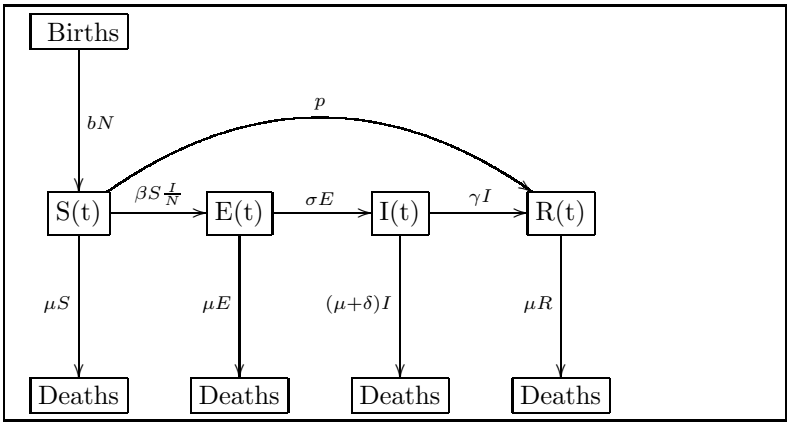
Therefore, we divide the population into five compartments : $S(t)$, $E(t)$, $I(t)$ and $R(t)$ as susceptibles, exposed, infectious and the immune individuals, where t represents the time. So, at time t an homogeneous population of size $N(t)$ is categorized to disease status :

- $S(t)$ = Susceptible individuals
- $E(t)$ = Exposed individuals, but not yet infectious
- $I(t)$ = Infectious individuals; they can spray the disease
- $R(t)$ = Recovered from disease or removed artificially trough vaccination are all permanently immune.

If β is the average number of adequate contacts (i.e., contacts sufficient for transmission) of a person per unit time, then $\beta\dfrac{I(t)}{N(t)}$ is the average number of contacts with infectives per unit time of one susceptible,

and $\beta\left(\frac{I(t)}{N(t)}\right)S(t)$ is the number of new cases per unit time due to the $S(t)$ susceptibles.

During this horizontal transmission, our deterministic, compartmental model is expressed by the following transfer diagram:



The parameters are defined as following :

β	Contact rate
$\frac{1}{\sigma}$	Average latent period
$\frac{1}{\gamma}$	Average infectious period
b	Birth rate
p	Proportion of those successively vaccinated at birth
μ	Mortality rate
δ	Differential mortality due to measles

In sub-saharan africa, vaccination against measles consists of one dose of standard titer Schwarz vaccine given to infants after 9 months of age. Nevertheless, during epidemics an early two-dose strategy was implemented : one dose between 6 and 8 months and one dose after 9 months ([6],[7]). Before this age, we suppose that children gain protection from the maternal antibodies.

Taking into account this schedule of vaccination, the differential equations for this deterministic model are as follows:

$$\begin{aligned} \frac{dS}{dt} &= b(1-p)N - \beta S\frac{I}{N} - \mu S \\ \frac{dE}{dt} &= \beta S\frac{I}{N} - (\sigma+\mu)E \\ \frac{dI}{dt} &= \sigma E - (\gamma+\mu+\delta)I \\ \frac{dR}{dt} &= bpN + \gamma I - \mu R \end{aligned} \tag{1}$$

3 Stability of the disease-free state

The Jacobian of (1) at the equilibrium point (S^*, E^*, I^*, R^*) is

$$J^* = \begin{pmatrix} b(1-p) - \beta\frac{I^*}{N^*} - \mu & \beta\frac{I^*}{N^*} & 0 & bp \\ b(1-p) & -(\sigma+\mu) & \sigma & bp \\ b(1-p) - \beta\frac{S^*}{N^*} & \beta\frac{S^*}{N^*} & -(\gamma+\mu+\delta) & \gamma + bp \\ b(1-p) & 0 & 0 & -\mu + bp \end{pmatrix}$$

In absence of infection $E^* = I^* = 0$, the Jacobian of (1) at the disease-free equilibrium $\mathcal{E}_0 = (S^*, 0, 0, R^*)$ is

$$\begin{pmatrix} b(1-p) - \mu & 0 & 0 & bp \\ b(1-p) & -(\sigma+\mu) & \sigma & bp \\ b(1-p) - \dfrac{\beta b(1-p)}{\mu} & \frac{\beta b(1-p)}{\mu} & -(\gamma+\mu+\delta) & \gamma + bp \\ b(1-p) & 0 & 0 & -\mu + bp \end{pmatrix}$$

Its eigenvalues are $\lambda_1 = -\mu$, $\lambda_2 = -(b-\mu)$ and the roots of

$$X^2 + (2\mu + \sigma + \gamma + \delta)X + (\sigma+\mu)(\gamma+\mu+\delta) - \frac{\beta b(1-p)}{\mu}$$

Theorem The disease-free equilibrium $\mathcal{E}_0$ is locally stable if $R_p < 1$ and unstable if $R_p > 1$ where

$$R_p = (1-p)\frac{b\beta\sigma}{\mu(\sigma+\mu)(\gamma+\mu+\delta)}$$

Proof: As λ_1 and λ_2 are negative, it remains to prove that λ_3 and λ_4, the roots of the quadratic part of that characteristic polynomial of J^* are both negative. We know that, using Routh-Hurwitz theorem, it is the case when

$$\lambda_3 + \lambda_4 < 0 \text{ and } \lambda_3\lambda_4 > 0.$$

As $\lambda_3+\lambda_4 = -(2\mu+\sigma+\gamma+\delta) < 0$ is true, we are done from $\lambda_3\lambda_4 = (\sigma+\mu)(\gamma+\mu+\delta) - \dfrac{\beta b(1-p)}{\mu} > 0$.

Remark:

- R_p is the effective reproduction number in presence of vaccination.
- If $p = 0$, we have the basic reproductive number $R_0 = \dfrac{b\beta\sigma}{\mu(\sigma+\mu)(\gamma+\mu+\delta)}$

4 Optimal vaccination strategies

4.1 Herd umminity

Herd immunity is the level of immunity in a population which prevents epidemics , even if some transmission may stilll occur. For instance, when a cohort of 500000 newborns benefit a 90% vaccine coverage, it yields 450000 vaccinated and 50000 unvaccinated. If vaccine efficacy is only 95%, it results 427500 immune and 22500 vaccinated but non-immune. Thus, it sums up to 427500 immune and 72500 susceptibles, and the corresponding herd immunity is 85.5%.

It well-known that the higher R_0 is for a disease, the higher the proportion of the population will have to bevaccined to achiev herd immunity([2]). Although, this statement could seem very theoretical, it was almost the perpective followed by WHO's Technical Working Group, when devising strategies to control a full range of diseases; for instance, this procedure has succeed during the worldwide campaign for smallpox eradication in the 1960s.

4.2 The condition for control

Let p be the proportion immune after a vaccination campaign. To reach the co-called critical proportion p_c, we need the control condition $R_0(1-p_c) < 1$ to fullfilled. It means

$$R_0(1-p_c) = 1 \Longleftrightarrow 1 - p_c = \frac{1}{R_0} \Longleftrightarrow p_c = 1 - \frac{1}{R_0}$$

For instance, in most sub-saharan Africa countries, the basic reproductive number for measles R_0 is approximately around 18 ([2], [7]), so $p_c = 0.94$.

Under the schedule of an unique dose, the minimal coverage to control measles is such that everyone does not need be immune through vaccination to control measles. We need high herd immunity to succeed control, it may require everyone receiving a 95% efficacious vaccine as

$$\text{coverage} \times \text{efficacy} = 0.94 \Longleftrightarrow \text{coverage} \equiv 0.99$$

We conclude that it's quite impossible via a single opportunity schedule.

4.3 What about the two opportunities schedule?

WHO's strategies for achieving sustainable reduction of measles mortality comprises a provision of a second opportunity for measles vaccination for all children through routine or supplemental activities. It come along routine immunization with one dose of measles vaccine administered at nine months of age or shortly thereafter.

In this framework, what coverage can be attained? Let v be the successful proportion vaccinated.

- v satisfies $v + v(1-v) = 0.94$ and $v = 0.76$.
- coverage $\times$ efficacy $= v = 0.76$
- To succeed controling measles, we need only vaccination coverage around 0.79 comparing to 0.99 obtained with one dose.

5 Discussion

It's very important to found that conceptual tool as R_0 can solve such concrete problem as devising optimal vaccination strategies for a all range of diseases. Theoretical determination of threshold conditions for R_0 is of important public heath interest. Nevertheless, this approch has limits due to the pattern of the transmission dynamics. For instance, it seems that it can't deal with non permanent infection-acquired immunity, such AIDS or Malaria.

We reach total agreement with WHO and UNICEF recommendations on measles control, as herd immunity increases with number of opportunity.

Mathematically, our results rely upon locally stability of the disease-free equilibrium point. We have studied the local stability of endemic equilibrium again by linearisation, Jacobian matrix and Routh-Hurwitz theorem. These techniques are not suitable to know if the free-disease equilibrium point is globally stable; in such case, the disease can be eradicated irrespective the initial sizes of the compartment, as encountered in the real situation. An other limitation is the lack of success when prospecting global stability for SEIR epidemiological models with non-constant population; are Lyapunov functions can be used successfully ?

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