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The probability of undetected wild poliovirus circulation: Can we do better?

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HIGHLIGHTS

- We compute the probability of silent infections as a function of free information.
- We show that including the date of the last paralytic WPV infection can be crucial.
- A vaccination strategy based on this information performs only slightly better.

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ABSTRACT

Acute flaccid paralysis surveillance actively detects new paralytic infections caused by wild poliovirus (WPV). However, most WPV infections occur with no symptom. This complicates determining when WPV is eradicated in the context of stopping oral poliovirus vaccine (OPV). Previous studies have used the time since the last paralytic infection as a variable of interest to construct this probability. In this study, we show that more freely available information can be used. In particular, we focus on enriching the computation of the probability of WPV silent circulation with the date of occurrence of the last paralytic infection. We show that this information can for at least one set of conditions have crucial importance for an accurate estimation of the risk of false positive when declaring WPV eradicated. We also look at the importance of this information for optimal dynamic vaccination strategies.

1. Introduction

The last known case of wild poliovirus (WPV) type 2 occurred in Northern India in 1999. Since then, surveillance of acute flaccid paralysis due to this strain of polio shows that undetected transmission should be non-existing. The last case of WPV type 3 was observed in the end of 2012, suggesting the possibility of the eradication of this strain as well (Kew et al., 2014). 4 of the 6 World Health Organization regions have been certified polio-free, indicating the absence of detected indigenous WPV transmission for at least 3 years. Circulation of WPV type 1 has not stopped yet and hence remains endemic according to the Global Polio Eradication Initiative only in Afghanistan, Nigeria and Pakistan.

These global successes, suggesting that the endgame is near, have been achieved by the use of two different polio vaccines (Duintjer Tebbens et al., 2005): inactivated poliovirus vaccine (IPV) and oral poliovirus vaccine (OPV). IPV is relatively harder to administer since it requires an injection and comes at a higher price than OPV that consists in simply two drops taken orally (Duintjer Tebbens et al., 2010). Moreover, OPV contains a live attenuated virus that provides immunity to symptomatic polio and better protection against intestinal reinfection than IPV (Duintjer Tebbens et al., 2013a). The attenuated virus contained in OPV can also spread to others and provide secondary immunity (Duintjer Tebbens et al., 2005; Onorato et al., 1991). However, as the live attenuated virus included in OPV circulates, it can undergo genetic mutations. In some rare[1] but still existing cases, the vaccine virus can be modified into circulating vaccine-derived polio virus (cVDPV) that can cause outbreaks with a rate of paralysis and transmissibility similar to WPV (Estivariz et al., 2008; Kew et al., 2002, 2004, 2005; Yang et al., 2003; Minor, 2009; Duintjer Tebbens et al., 2013a, 2013b). Hence, if OPV provides the benefit of protecting against paralysis in the first place, it comes with the price of creating new paralysis in the long run if population immunity does not remain high enough. Therefore, it is now acknowledged that eradicating symptomatic poliovirus infections

[1] According to WHO, 10 billion doses of OPV have been administered to nearly 3 billion children worldwide between 2000 and 2014. During the same period, 20 cVDPV outbreaks occurred in 20 countries. See http://www.who.int/features/qa/64/en/ retrieved on January 5, 2015.

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will require stopping OPV use as early as possible (Thompson et al., 2008; WHO, 2010, 2005; Tebbens et al., 2006; Thompson and Duintjer Tebbens, 2008; Aylward et al., 2005).

Then, in this epidemiological setting, the question of knowing when to stop the OPV vaccination effort becomes a relevant and crucial optimization problem (Smith et al., 2004; WHO, 2004). If all WPV infections could be observed, the answer would be simple since the costs and benefits of stopping the OPV vaccination effort would be straightforward. However, typical estimates suggest that paralysis comes with WPV infection at a rate of approximately 0.5% (with large differences between serotypes) for fully susceptible individuals (Bernier, 1984; Nathanson and Kew, 2010). The rest of poliovirus infections occurs with no symptom. Thus, even in the absence of observed paralytic infections, there is still a risk of silent WPV circulation (CDC, 2005, 2008).

It is this risk that is studied in Eichner and Dietz (1996) and extensively discussed, criticized and whose evaluation robustness is checked in Kalkowska et al. (2012). These analyses consider a period of 10 years after the start of an OPV vaccination effort (with 60% effective routine coverage at birth) in a population of 200,000 homogeneously mixed individuals with a yearly 2% growth. Using a very simple, compartmental, dynamic and stochastic model, Eichner and Dietz (1996) showed that not observing a paralytic infection for 2.9 years provides a 95% confidence in the eradication of WPV. Kalkowska et al. (2012) showed that this quantitative result is highly dependent on initial conditions and seasonality of the basic reproduction numbers.

Even though our standpoint is different from Kalkowska et al. (2012), we also use the study by Eichner and Dietz (1996) as a starting point. We consider the same simple model and the same initial conditions and ask the question of the value of the information we have access to in this setting. We show that knowing the time passed since the last paralytic infection should be accompanied by the date[2] of occurrence of this last paralytic infection for much greater accuracy in the estimation of the probability that WPV is still silently circulating. More precisely, we show that not observing a paralytic infection for 2.9 years can provide a confidence as low as 80% or as high as 97% in the eradication of WPV, depending on the date of occurrence of the last paralytic infection. The reason for this result is that the dynamics of the compartmental model after the start of the OPV vaccination effort is oscillating with a large and damped amplitude. Because the oscillations are damped, when WPV is eradicated, this occurs with a very high probability around the first lowest point of the oscillation and Eichner and Dietz (1996)'s result should be seen as an average with a great weight at that point but with very different values in different points of the oscillatory process. This intuition is implicitly suggested in Kalkowska et al. (2012). They show that changing the initial conditions reduces the amplitude of the oscillations of the polio dynamics, leading to a dramatically lower probability to ever see WPV eradicated. However, changing the initial conditions does not modify much the time without any paralytic infection required to have a 95% confidence in the eradication of WPV. The oscillatory nature of the polio dynamics after introduction of the OPV vaccination effort has also been studied in Mayer et al. (2013) in a different context.

Our results show that the date of the last paralytic infection is a crucial and free piece of information that should be considered. By taking advantage of our understanding of the oscillatory nature of the dynamics of the disease, it helps giving more accurate results for an informed policy recommendation.

[2] Dates are to be understood as the time passed since the beginning of the eradication program.

Table 1
Parameters value for the simulations.

Parameter	Dimension	Value	Description
N	1	200,000	Initial population size
α	year^{-1}	0.02	Population growth rate
μ	year^{-1}	1/45	Death rate
ν	year^{-1}	$\mu+\alpha$	Population birth rate
p	1	0.6	Fraction of newborns successfully vaccinated at birth
δ	day^{-1}	1/3.5	$2\times$ transition rate from incubation period
γ	day^{-1}	1/15	$2\times$ transition rate from infectious period
R_0^{WPV}	1	12	Basic reproduction number for WPV
b	1	1/4	Relative infectivity of OPV compared with WPV
PIR	1	1/200	Paralysis to infection ratio

2. Material and results

In this study, we use the exact same compartmental, stochastic and dynamic model as in Eichner and Dietz (1996), see Section A.1. We also use the same base-case parameters, see Table 1, and the vaccination-free stationary state as an initial condition. However, for each simulation run, we make the stochastic model run for a one-year period before introducing OPV vaccination in order to have a realistic variability in the actual initial state of the population.[3] We run 2,000,000 simulations of the model for a 30-year period (after the start of the OPV vaccination effort) using a Gillespie algorithm (Gillespie, 1976).

Let us assume that the OPV vaccination effort starts at time 0. Like in Eichner and Dietz (1996), we assume that a paralytic infection is also observed at time 0 for initialization. We denote $P(t)$ the empirical probability that, even though no paralytic infection has been observed for t months,[4] WPV is still circulating, *i.e.*, there is still at least one individual in WPV incubating or infectious compartments. $P(t)$ is called the "probability of silent infections" and it is a function of the time passed since the last paralytic infection as computed in Eichner and Dietz (1996).

In this paper, we consider that we may actually have more information at our disposal than just the time passed since the last paralytic infection. We denote $P^+(t,t')$ the empirical probability of silent infections as a function of both the time passed since the last paralytic infection, t, and the date of occurrence of this last paralytic infection, t', to be understood as the time passed between the start of the eradication program and the last observed paralytic infection, see Figs. A1 and A2. As we will see, this added piece of information – the date of occurrence of the last paralytic infection – can be very valuable in assessing successful eradication. Let us develop some intuition by looking at the deterministic evolution of the disease displayed in Fig. 1.

Before the OPV vaccination effort starts, about 3.3 paralytic infections occur each month. After the start of the OPV vaccination effort, the number of paralytic infections decreases sharply for about 2 years. For the following 3 years, it remains practically null. For this period, the deterministic simulation and the empirical average over our 2,000,000 stochastic simulations give very similar results. 5 years after the start of the OPV vaccination effort, the number of paralytic infections given by the deterministic model increases and decreases again with a wavelength of about

[3] Then, at the time of the introduction of the OPV vaccination effort, the population whose yearly growth is 2%, is composed, on average, of about 204,000 individuals.

[4] Notice that in all this paper, "empirical" refers to the results of the stochastic model simulations and not to any data observed in the real world. Also, unless stated explicitly, all times are expressed in months.