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Statistical certification of eradication of poliomyelitis in the Americas

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Abstract

The last confirmed case of paralytic poliomyelitis due to indigenous wild poliovirus in the Americas occurred in Peru in 1991. In 1994 the International Commission on Polio Eradication of the Pan American Health Organization (PAHO) deemed eradication of polio from the area to have occurred, based on its strategic efforts and the observed results. A mathematical model is presented here which relates the time elapsed since that last detected case of paralytic poliomyelitis caused by wild poliovirus to the probability that the transmission of indigenous wild poliovirus has been stopped. The appropriateness of applying the model to various geographical areas of the Americas is investigated using data about the occurrence of confirmed cases of polio since 1984, the time of the eradication initiative adopted by PAHO. The model suggests that if four years have elapsed since the last reported confirmed case of polio caused by wild poliovirus, and no other confirmed cases have been identified, the probability of undetected indigenous wild poliovirus transmission is less than 5%. An important assumption is that the eradication strategy implemented by PAHO has yielded steady improvements. A consequence of this approach is that the annual probabilities of persistence given by the model are conservative, in the sense of being higher than the true, but unknown a priori probabilities, and more so with each passing year. It is thus seen that the model results are compatible with the conclusion reached by PAHO in 1994. The model takes into account the intensity of surveillance of each country in the region, measured by the corresponding rates of acute flaccid paralysis (AFP). Because importations of wild poliovirus may occur from other regions of the world, surveillance efforts are being maintained in the Americas until global eradication has been achieved.

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1. Introduction

The last confirmed case of paralytic poliomyelitis due to indigenous wild poliovirus in the Americas was identified on 5th September 1991 in Junin, Peru [1,2]. Poliomyelitis, once so greatly feared, is thought to have been eradicated from the Americas.

The eradication initiative adopted by the Pan American Health Organization (PAHO) in 1985 called for the eradication of polio through interruption of the chain of transmission of indigenous wild poliovirus [3]. The International Certification Commission on Polio Eradication (ICCPE) of PAHO [4] has deemed eradication to have occurred based on its strategic efforts [5], which are briefly described in Section 2, and the observed results.

In 1993, the ICCPE commissioned the authors of this paper to mathematically estimate the length of time without confirmed cases in the region that would have to be observed before eradication should be considered to have been achieved. This paper describes the result of this investigation: a mathematical model, useful for estimating this length of time, which is found to agree with observed historical data. Based on this model, we coined the term 'statistical certification of eradication' to convey the notion that, except for an acceptably small probability, the virus is inferred not to persist.

It must be stated that the specific actions taken as part of the polio eradication strategy have an indirect, but crucial, role in the derivation of certain estimates presented here. An assumption made in deriving the key expression for an upper bound for the likelihood of persistence, for instance, is that those parts of the eradication strategy dealing with vaccinations and surveillance have resulted in 'steady' improvements. If that is the case, then, the likelihood of individuals remaining free from infection as well as that of detecting (locating and confirming) cases should increase over time. An important consequence of this approach is that the estimates of the probabilities of persistence provided are conservative, in the sense that the true, but unknown, a priori probabilities are lower than those predicted by the model and more so with passing years.

We first pose the problem for a hypothetical geographical region with a stable population and then apply the model to provinces and countries, testing assumptions against annual numbers of confirmed cases. The model is then refined to take into account the intensity of surveillance as indirectly indicated by background incidence rates of acute flaccid paralysis (AFP).

Ultimately, we propose the relatively simple result that for a country in the Americas, incorporating the net effect of the strategy of polio eradication on

the country's specific features, including adequate surveillance, there is less than a 5% chance that eradication has not occurred given that there have occurred at least four years without a confirmed case of poliomyelitis transmitted by indigenous wild poliovirus.

The present paper is based on the report that we presented to the ICCPE in 1993 [6], with updates of some empirical probabilities.

2. The eradication initiative

Poliomyelitis is an acute infectious disease caused by polioviruses, of which there are three serological types. In its most serious clinical manifestation it affects the central nervous system and may result in flaccid paralysis. By far, however, the most common manifestation is a mild febrile or even a silent subclinical episode.

The poliovirus inhabits the alimentary tract of humans, who are its only natural hosts. Transmission of the virus occurs through the oral-fecal route, mostly from person to person contact and primarily due to fecal contamination, a result of infected individuals shedding large numbers of viruses in their stools. Evidence of infection in the community is provided by the finding of the virus in stools of apparently healthy individuals and in community sewage. Systematic and frequent sampling of wastewater of affected communities has led to excellent characterization of the frequency and pattern of occurrence of viruses in sewage systems. The findings have been used to estimate the ratio of infections to clinical disease.

Evidence of clinical disease is provided by the occurrence of AFP in which the poliovirus is isolated from stools of the affected individual. The latter condition is important since AFPs can be caused by other agents. A case of AFP is classified as a 'confirmed' case of poliomyelitis if it is associated with wild-type poliovirus laboratory isolation. A case of AFP is classified as 'compatible' (with being a case of poliomyelitis) if there is a lack of two adequate stool samples and there is resultant residual paralysis or death or if there is no timely follow-up.

There are large variations in the pattern of disease occurrence, dependent upon person characteristics, geographic location, season of year and vaccination program. But in general, in a post-vaccination phase, after repeated mass vaccination campaigns reach practically all children and cases of paralytic polio are rare occurrences, 'wild' indigenous polioviruses are rarely found, and most viruses that are isolated in the laboratory are either imported wild polioviruses or belong to vaccine associated strains. Imported viruses can be identified as such because of the distinctive geographic distribution of the three serological types mentioned above.

In 1985, PAHO initiated a campaign to eradicate polio from the Americas, with eradication being defined as the interruption of the indigenous

transmission of wild poliovirus. The ICCPE of PAHO, established in 1990, divided the Americas into seven major areas, each comprising one or more countries, assigning one or two of the Commission's members to oversee certification procedures of each area. Areas were considered eligible for certification only when all their member countries could demonstrate interruption of transmission. Certification of eradication for the Americas occurred when every area succeeded in demonstrating eradication.

Common principles of the surveillance systems of the various countries included having a hierarchical weekly reporting system, starting with at least one health agency identified in each county (or equivalent small geopolitical entity) reporting to the state or provincial level agencies, these reporting to the national level agencies and national authorities reporting to PAHO headquarters. Specially trained epidemiologists attempted to investigate every case of reported AFP within 48 h of notification.

At the country level, four strategic issues were identified as essential for qualifying for certification of eradication: (1) surveillance of AFP cases, (2) surveillance of wild poliovirus, (3) active AFP case searches in areas of risk, such as in areas where confirmed or compatible cases occurred in the past or where reports were not received, and (4) documentation of mass immunization (or mop-up) campaigns in areas of risk.

As mentioned above, for poliomyelitis, unlike for smallpox, there exists a much larger proportion of asymptomatic infections compared to clinical cases. One challenge for the polio eradication initiative was to verify the absence of infections in otherwise healthy children of the community. Three strategies were used for surveillance of wild poliovirus: the timely collection and processing of stool samples of AFP cases, stool surveys of normal children during investigations of contacts of cases and sampling of community wastewater for the presence of wild poliovirus.

Active case searches in areas of risk had to be documented using standardized methods, with particular emphasis on identification of areas of risk and adequate methods of data collection and analysis.

Mop-up, or door-to-door, immunization campaigns played a key role in the eradication campaign. Several considerations dictated their conduct. One was the recognition that certain small areas within countries could have inferior surveillance efforts without markedly affecting overall quality of indicators. Other targeted areas were those where compatible cases recently occurred. Unstable areas of civil disorder, refugee populations, heavy migration and border locations were also particularly targeted.

Cuba was one of the first countries to interrupt the chain of transmission of the virus and one of four countries, along with the Dominican Republic, Nicaragua and Paraguay, in which the door-to-door immunization campaign for all children under six years of age, regardless of immunization status, was empirically found to be highly effective for this purpose. In those countries, trans-

mission was interrupted in two years, while other countries without this strategy took longer to do so. This strategy was adopted by the ICCPE and used in every country, concluding with the massive mop-up campaign following the last reported case of polio in 1991, in which 2 000 000 households of eastern Peru were covered in one week. The aggressiveness of the campaign was motivated by the huge north–south displacements of people in that part of the country caused by civil unrest.

3. Data considerations

In the construction of this mathematical model, the level of detail was suggested by the nature of data available for testing the model, as well as logistical concerns. Since the time period of interest is related to the intensive eradication efforts proposed in 1985 [3,7], the time parameters of formulas in the model are understood to refer to times no earlier than 1986. Most of the probability statements treat time as discrete calendar year units, so that we utilize the precision of demographic language to specify the populations to which references are made.

Statements about confirmed cases of poliomyelitis transmitted by wild poliovirus implicitly assume the case definitions used by PAHO at that time. The available data gives counts of confirmed as well as compatible cases. The model presented here addresses the chances of eradication of wild poliovirus based on observations of annual numbers of confirmed cases. Although at this time the probability that a 'compatible' case is really a polio case is unknown, we are able to show that the model structure holds when compatible cases are treated as true cases. The model does not distinguish among wild poliovirus genotypes, although it is noted that the three genotypes have very different geographical distributions.

Numbers of incident cases and numbers of prevalent infected individuals refer to such occurrences at any time during a year. Issues related to the number of susceptibles are discussed in the context of the disease moving toward eradication, so that consideration is given only to localized areas where somewhat recent detection of wild poliovirus has occurred, and without consideration of age.

Issues of periodicity are outside the scope of this paper other than to note that an inter-epidemic period of three to five years is suggested by a study of data from England and Wales which is consistent with estimates of four to five years suggested by mathematical modeling techniques [8].

4. The theoretical model

Let us first consider an isolated geographical region with a stable population in the Americas. Isolation removes the need to consider immigration,

emigration and transmigration. We are concerned with members of the population at any given time, if any, who are infected with indigenous wild poliovirus.

We assume the existence of a suitable probability space upon which to define separable stochastic processes. Define $N(t)$ to be the total number of infected individuals in the region at time t (where, for example, $t = 1986$ means the end of the year, 1986) and let $\xi(t)$ be the length of time since the last confirmed case prior to time t in the region due to wild poliovirus. When examining data, we approximate $\xi(t)$ by the number of full calendar years having elapsed since a confirmed case. $N(t)$ can be characterized as a stochastic process defined over continuous time and with a sample space consisting of the non-negative integers.

Next, define the one year maximum and minimum

$$M(t) = \max[N(s):\ t-1 \leqslant s \leqslant t],$$

$$m(t) = \min[N(s):\ t-1 \leqslant s \leqslant t],$$

respectively, and, similarly, for $k \geqslant 0$ define the k year maximum and minimum

$$\ddot{M}(t,k) = \max[N(s):\ t-k \leqslant s \leqslant t],$$

$$\ddot{m}(t,k) = \min[N(s):\ t-k \leqslant s \leqslant t], \text{respectively.}$$

These are the highest levels and lowest levels that have been reached by $N(t)$ in the last year, or k years, respectively, prior to time t.

Using this notation, we can formally address the issue of eradication of disease at a time t. We shall say that statistical certification of eradication has occurred when the number of years, k, observed without detection of any cases, is such that

$$P\{N(t) > 0 \mid \xi(t) = k\} \tag{1}$$

is sufficiently small, operationalized as being less than 5%.

It is important to recognize the existence of two threshold levels which help to define events important to eradication or persistence. The three events under which the wild poliovirus may persist in this population are as follows:

1. prevalence of infection with the wild poliovirus does at times exceed a threshold level such that the number of subsequently developing cases is sufficient for likely detection; however, against those odds, surveillance fails to confirm a single case;
2. without ever exceeding the above threshold level, infection with the wild poliovirus may at times drop in prevalence to below a threshold level where the virus is unlikely to persist; however, against those odds, persistence occurs;
3. the number of infected individuals fluctuates between the upper threshold mentioned in (1) and the lower threshold of (2), never producing enough cases for likely detection nor leaving so few infected individuals that there is little likelihood of persistence of the wild poliovirus.

It is noted that the above three events are mutually exclusive in a region, qualitatively describing events which are the only ways for the wild poliovirus to persist. Therefore, given the occurrence of k successive years without detection of a confirmed case, the probability of persistence is the sum of the probabilities of those three types of events.

In the approach taken here, the fact that the two thresholds exist at any one time is more important than their specific values. We interpret them to be those values sufficiently extreme as to make the joint occurrence of crossing them and undetected persistence of the virus very unlikely for a region. The notion that the threshold values are based on the realities of a region is consistent with our approach, in which we estimate probability upper bounds using regional empirical data.

4.1. The upper threshold

The upper threshold level is based on the number of cases that would need to occur for the chances to be negligible of surveillance efforts failing to detect a single confirmed case. In the context of eradication, we are interested in the number of infected individuals, rather than cases of disease, but the existence of an upper threshold for clinical cases implies the existence of a corresponding upper threshold for infections because the relationship between the number of cases and the number infected for a given wild virus genotype is known (taken to be between 1:100 and 1:1000, depending on wild virus genotype).

Let B refer to this upper threshold of infected individuals, corresponding to a number of cases highly unlikely to go undetected by the surveillance system in place. Since the number of actual cases sufficient to make detection likely must be at least one or two, we might anticipate a value of B to be in the hundreds or thousands; however, the intensity of the surveillance operations suggest that the value of B above which detection is likely to occur could be much smaller. Depending on the intensity of sampling and the level of development (i.e., indoor plumbing throughout), the value of B for likely detection could well be of the order of tens of people. We define B to be the smallest integer for which

$$P\{N(t) > 0 \text{ and } \ddot{M}(t,k) > B \mid \xi(t) = k\} < 0.005 \quad (k \geqslant 3). \tag{2}$$

4.2. The lower threshold

On the other extreme, it has been established that for a microparasite to remain endemic in a host population, there is a threshold (minimal level of people carrying the wild poliovirus below which 'endemic fade-out' occurs) required for the virus to maintain itself [9]. In the case of poliomyelitis, it has been suggested [8] that the threshold level, b, is of the order of 20–100

infected individuals in the host population for the virus to persist, with or without immunization efforts in place. The scarcity of susceptibles in a region with an active immunization program makes the event of actually reaching the threshold number of infected individuals less likely. We define b to be the greatest integer for which

$$P\{N(t) > 0 \text{ and } \ddot{m}(t,k) < b \mid \xi(t) = k\} < 0.005 \quad (k \geqslant 3). \tag{3}$$

4.3. The middle range

We have discussed the existence of a level B, above which the number of individuals carrying the wild poliovirus will almost surely be detected by surveillance activities, and of a level b, below which the phenomenon of "endemic fade-out" will likely occur.

The middle range event is the event where the number of infected individuals never exceeds B nor drops below b for k years given the conditioning event that no confirmed cases have been detected for the k years.

4.4. Mathematical specification of the model

Let us assume that given any t_0, $N(t_0) = n_0, \xi(t_0) = k_0$ and that $N(t)$ $(t \geqslant t_0)$ is a stochastic process with independent increments. Further, assuming that the region's social mixing characteristics are such that the effective size of an individual's contact group is S_0, other individuals among whom social mixing can occur, then with complete random mixing of individuals homogeneously over time (and assuming that S_0 are susceptibles), it would follow [10] that for small $\Delta t > 0$,

$$P\{N(t_0 + \Delta t) - N(t_0) = 1 \mid \xi(t_0) = k_0\} \approx n_0 S_0 \lambda_0 \Delta t, \tag{4}$$

$$P\{N(t_0 + \Delta t) - N(t_0) = -1 \mid \xi(t_0) = k_0\} \approx n_0 \mu_0 \Delta t, \tag{5}$$

$$P\{N(t_0 + \Delta t) - N(t_0) = 0 \mid \xi(t_0) = k_0\} \approx 1 - n_0 \Delta t (S_0 \lambda_0 + \mu_0), \tag{6}$$

and other events for $\{N(t_0 + \Delta t) - N(t_0) \mid \xi(t_0) = k_0\}$ have approximately zero probability, where μ_0 is a Poisson parameter representing mortality among those infected at time t_0 and λ_0 is that Poisson parameter representing the effective force of infection given physical interactions and mixing at time t_0, interpersonal habits that might allow transmission of the wild poliovirus and local polio control efforts.

At other points in time, $t_j > t_0 (j = 1, 2, \ldots)$, where it is given that $N(t_j) = n_j, \xi(t_j) = k_j$, the effective number of susceptibles are still S_0, and μ_j and λ_j are the respective values of the Poisson parameters at time t_j, it follows that for small $\Delta t > 0$:

$$P\{N(t_j + \Delta t) - N(t_j) = 1 \mid \xi(t_j) = k_j\} \approx n_j S_0 \lambda_j \Delta t, \tag{7}$$

$$P\{N(t_j+\Delta t)-N(t_j)=-1 \mid \xi(t_j)=k_j\} \approx n_j\mu_j\Delta t, \tag{8}$$

$$P\{N(t_j+\Delta t)-N(t_j)=0 \mid \xi(t_j)=k_j\} \approx 1-n_j\Delta t(S_0\lambda_j+\mu_j), \tag{9}$$

and other events for $\{N(t_j+\Delta t)-N(t_j) \mid \xi(t_j)=k_j\}$ have approximately zero probability. Thus, precise specification of the finite dimensional distribution functions for $N(t)$ would require exact knowledge of how the Poisson parameters, μ_j and λ_j change over time. It is reasonable to assume that the Poisson parameters vary slowly and that N_j and S_0 have small proportional changes over time, because the forces of mortality and social mixing are slow to change. The discrete changes to $N(t)$ occur at random times, determined by the occurrence of either of the Poisson events. The probabilities of increase or decrease given the occurrence of a change is based on the relative fraction of Eq. (7) or Eq. (8), respectively, of the sum of the quantities in Eqs. (7) and (8), independently of Δt. We assume in the sequel that we are not dealing with the trivial situation with overall drift, i.e., where the quantity in Eq. (7) exceeds that in Eq. (8) when $n_0 = B$ or where the quantity in Eq. (8) exceeds that in Eq. (7) when $n_0 = b$.

Let us use the notation $W(t)$ to refer to the version of the stochastic process, $N(t)$, which contains an imbedded Markov Chain which is a symmetric random walk. The imbedded Markov Chain is the stochastic sequence of the states of the process immediately after each (Markov time) epoch of change [11]. $W(t)$ can be seen to be a special case of $N(t)$ by requiring

$$S_0\lambda_j = \mu_j (j = 0, 1, 2, \ldots).$$

The right-hand sides of Eqs. (4) and (5) are equal as are those of Eqs. (7) and (8). This says that the chances of increase and decrease are the same in the imbedded Markov Chain, each equal to $\frac{1}{2}$.

Lemma 1. *The quantity*

$$P\{N(t)>0 \text{ and } \ddot{M}(t,k)\leqslant B \text{ and } \ddot{m}(t,k)\geqslant b \mid \xi(t)=k\} \quad (k\geqslant 3), \tag{10}$$

is maximized when $N(t) = W(t)$, that is, when $N(t)$ has an imbedded symmetric random walk.

Proof. Let $\zeta(t,k)$ be the number of changes of the process $N(t)$ in the time from $t-k$ to t. We will prove the lemma by induction on $\zeta(t,k)$.

For the inductive step, $\zeta(t,k)=1$ we note that the complementary event to

$$\{N(t)>0 \text{ and } \ddot{M}(t,k)\leqslant B \text{ and } \ddot{m}(t,k)\geqslant b \mid \xi(t)=k \text{ and } \zeta(t,k)=1\} \quad (k\geqslant 3),$$

consists of sample paths in which $N(t)$ changes value only once in k years, starting either outside the boundaries or at a boundary b or B and, in the single change, crossing the boundary. The situation where sample paths start outside the boundaries is assumed to be much less likely and not dependent on

Eqs. (7)–(9). For the situation starting on a boundary, the difference in probabilities relates only to the single transition at the boundary, where without drift, crossing the boundary is less likely in the imbedded symmetric random walk situation. The symmetric situation clearly has smaller probabilities for the complementary event; thus, the lemma is true when $\zeta(t,k)=1$.

Suppose the lemma is true for values of $\zeta(t,k)=1,2,\ldots,K$. Because the initial conditions and the sample paths do not depend on whether or not $W(t)=N(t)$, the only differences will be in how probabilities of events (as well as of individual sample paths or sets of sample paths) are evaluated near the boundaries, b and B. As before, focusing on complementary events, we see that any such paths starting at $N(t-k)=n_0$ with $\zeta(t,k)=K+1$ must have the situation where a boundary is exceeded and for which it is first exceeded at the $K+1$ change or earlier. We will show the lemma is true for $\zeta(t,k)=K+1$ when the boundary B is crossed and note that the situation for b follows in a parallel manner. Define $C=\{N(t)>0$ and $\ddot{M}(t,k)>B$ and $\ddot{m}(t,k)\geqslant b \mid \xi(t)=k$ and $\zeta(t,k)=K+1\}$, which may be expressed as the disjoint union of

$$C\cap\{\ddot{M}(\tau_K,k-(t-\tau_K))\mid \xi(t)=k \text{ and } \zeta(t,k)=K+1\},$$
$$C\setminus\{\ddot{M}(\tau_K,k-(t-\tau_K))\mid \xi(t)=k \text{ and } \zeta(t,k)=K+1\},$$

where τ_K is the epoch of occurrence of the Kth change and the symbol '\' is taken to mean 'intersection with the complement of', above. The former set contains sample paths which, ignoring the last change, correspond exactly to sets of sample paths for which the lemma is true by the inductive assumption. Ignoring the last change means that events occurring on the $K+1$ change do not affect the relative probabilities. For the latter set, the lemma is true for the same reasoning as for the $\zeta(t,k)=1$ case.

Since the lemma holds conditionally on $\zeta(t,k)$ and the probability distribution of $\zeta(t,k)$ is independent of whether $W(t)=N(t)$, the lemma is true. □

We next use the symmetric random walk model to establish a geometric upper bound for Eq. (1), the probability of persistence. In some situations, that upper bound may be conservative, but it is esthetically pleasing that a single upper bound would serve as an effective upper bound for all situations.

Lemma 2. *The difference between Eq. (1) and Eq. (10) is less than* 1%.

Proof.

$$\begin{aligned}P\{N(t)>0\mid\xi(t)=k\}\leqslant\ & P\{N(t)>0 \text{ and } \ddot{M}(t,k)>B\mid\xi(t)=k\}\\ &+P\{N(t)>0 \text{ and } \ddot{m}(t,k)<b\mid\xi(t)=k\}\\ &+P\{N(t)>0 \text{ and } \ddot{M}(t,k)\\ \leqslant\ & B \text{ and } \ddot{m}(t,k)\geqslant b\mid\xi(t)=k\}.\end{aligned}$$

By Eqs. (2) and (3), the lemma is true. □

This shows, then, that given that there have been k years without a confirmed case, the persistence of the wild poliovirus (i.e., the event in Eq. (1)) is the disjoint union of persistence of the wild poliovirus without the process ever leaving the interval from b to B (i.e., the event in Eq. (2)) and persistence of the wild poliovirus with the process leaving that interval (i.e., an event with near zero probability).

In the following lemma we prove a simple version of the reflection principle for our imbedded symmetric random walk with a variation of a remark by Feller ([11], pp. 171–172) adapted to our situation.

Lemma 3. *For* $N(t) = W(t)$

$$P\{\ddot{M}(t,k) > x \mid \xi(t) = k\} \geqslant 2\, P\{N(t) > x \mid \xi(t) = k\} \tag{11}$$

for $b \leqslant x \leqslant B$.

Proof. Let τ denote the first time $N(s) = W(s) = x$ $(t - k \leqslant s \leqslant t)$. By symmetry the probability that $W(t) - W(\tau)$ is positive has the following property.

$$P\{W(t) - W(\tau) > 0\} = \tfrac{1}{2}(1 - P\{W(t) - W(\tau) = 0\}) \leqslant \tfrac{1}{2}.$$

Since the conditioning on $\{\xi(t) = k\}$ does not affect the symmetry, it follows that

$$\begin{aligned} P\{W(t) - W(\tau) > 0 \mid \xi(t) = k\} &= \tfrac{1}{2}(1 - P\{W(t) - W(\tau) \\ &\quad = 0 \mid \xi(t) = k\}) \leqslant \tfrac{1}{2}. \end{aligned}$$

Multiplying each side by $P\{\tau < t \mid \xi(t) = k\}$ yields the desired result. □

That is, the probability that the process exceeds a given level, x, at the end of an interval of fluctuation is at most half of the probability that the maximum level of the process ever exceeded x over the interval of fluctuation.

In the following theorem we establish a geometric upper bound for the conditional probability of persistence of the wild poliovirus.

Theorem 1. *For* $N(t) = W(t)$

$$P\{N(t) > 0 \mid \xi(t) = k\} \leqslant \tfrac{1}{2}(P\{b < M(t - k + 1) \leqslant B \mid \xi(t) = k\})^k. \tag{12}$$

Proof. We intend to examine B and b as reflecting barriers between which the position of $N(t) = W(t)$ is undergoing random fluctuations.

We express the maximum over the entire period in terms of the yearly maxima, noting that when the maximum over a period of years lies in an interval, then one of two situations must occur. Either each and every yearly maximum lies in that interval or else there are some years when the yearly maximum is less

than the smallest point in the interval, because the process has crossed to below that point. From Eq. (11) we write

$$P\{b < N(t) \leqslant B \mid \xi(t) = k\} = \frac{1}{2} P\{b < \ddot{M}(t,k) \leqslant B \mid \xi(t) = k\}$$
$$\approx \frac{1}{2}\left[P\left\{ \bigcap_{j=1}^{j=k} (b < M(t-k+j) \leqslant B) \mid \xi(t) = k \right\} + P\left\{ \bigcup_{i=1}^{i=k-1} C_i \text{ and } b < N(t) \leqslant B \mid \xi(t) = k \right\} \right], \tag{13}$$

where $C_i = C_i(t,k)$ denotes the event that the process has crossings to below the level of endemic fade-out during precisely i of the k calendar years subsequent to t. Stated more formally, $C_i = C_i(t,k)$ is the event that for precisely i of the $k-1$ intervals

$$(t-k, t-k+1), (t-k+1, t-k+2), \ldots, (t-2, t-1),$$

it is true that for some s in the interval $N(s) \leqslant b$. Note that this is not setting i to be the number of crossings (more specifically down-crossings) to below b; however, at least one such down-crossing must occur for the event, C_i, to occur ($i \geqslant 1$). Because the process $N(t) = W(t)$ is a stochastic process with independent increments and the intervals

$$(t-k, t-k+1), (t-k+1, t-k+2), \ldots, (t-1, t),$$

are disjoint, the behavior of the process in any interval is independent of its behavior in any other intervals. Because of this independence, the probability of the first (intersection) expression on the right-hand side of Eq. (13) is a product of probabilities

$$P\left\{ \bigcap_{j=1}^{j=k} (b < M(t-k+j) \leqslant B) \mid \xi(t) = k \right\}$$
$$\approx P\left\{ b < M(t) \leqslant B \mid \bigcap_{j=1}^{j=k} (b < M(t-k+j) \leqslant B) \text{ and } \xi(t) = k \right\}$$
$$\times P\left\{ b < M(t-1) \leqslant B \mid \bigcap_{j=1}^{j=k-1} (b < M(t-k+j) \leqslant B) \text{ and } \xi(t) = k \right\}$$
$$\times P\{b < M(t-k+1) \leqslant B \mid \xi(t) = k\}$$
$$\approx \prod_{j=1}^{j=k} P\{b < M(t-k+j) \leqslant B \mid \xi(t) = k\}$$
$$\leqslant \prod_{j=1}^{j=k} P\{b < M(t-k+1) \leqslant B \mid \xi(t) = k\}$$
$$= (P\{b < M(t-k+1) \leqslant B \mid \xi(t) = k\})^k. \tag{14}$$

Because the C_i terms on the right-hand side of Eq. (13) are mutually exclusive, the second (union) expression is a sum, each summand being a negligible probability from the definition of b,

$$P\left\{\bigcup_{i=1}^{i=k-1} C_i \text{ and } b < N(t) \leqslant B \mid \xi(t) = k\right\} \leqslant P\left\{\bigcup_{i=1}^{i=k-1} C_i \mid \xi(t) = k\right\} \approx 0. \tag{15}$$

Thus, from Eqs. (13)–(15)

$$P\{N(t) > 0 \mid \xi(t) = k\} \leqslant \frac{1}{2}(P\{b < M(t-k+1) \leqslant B \mid \xi(t) = k\}^k,$$

that is, the probability of persistence given that k years have elapsed without a confirmed case in the region has a geometric upper bound, a constant times some expression raised to the power k. □

5. Numerical results

We now turn to the available data on occurrences of confirmed cases of polio to see if observations are consistent with the structure of the model and, if so, to obtain numerical estimates of model parameters.

There are two issues to consider in the utilization of data. The first one is whether data are available. The other is the extent to which a particular geographical area which has yielded usable data can be thought of as having the necessary attributes, from the perspective of stability of population and commitment to the eradication program. With respect to available data, it would make most sense first to examine provinces as instances of regions, then countries, then continents and ultimately the Americas as a whole.

Some limiting factors need to be considered. With respect to the first issue, the available data at the province level is too limited to allow consideration of precise periods of interest with no confirmed cases. Instead, then, we first look at the country level data and then examine the consistency of findings with the scantier province level data. Applicability of country level findings to the three continents of the Americas is a direct consequence of the fact that the final stages of eradication have involved only a single country, as expected.

Regarding the second issue, as noted earlier, the eradication initiative has principles common to all areas of the Americas and based on indicator measures such as AFP rates and fraction of stool samples examined, the surveillance efforts have continued, unabated, at both the province and national levels. The lack of reported cases in the last stages of eradication has to be evaluated in light of the sustained level of surveillance efforts. This can be seen in Fig. 1, where the number of stool specimens tested has steadily increased over time.

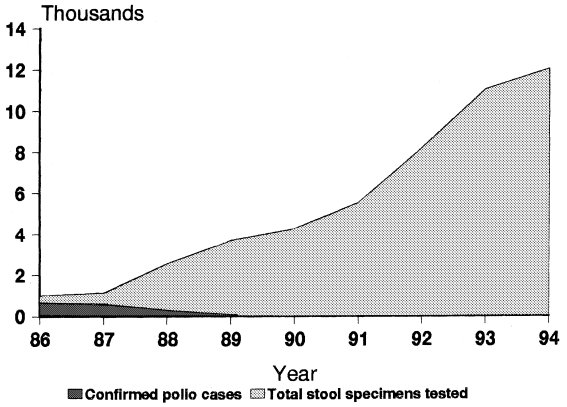

Fig. 1. Wild poliovirus surveillance in the region of the Americas, 1986–1994. For 1994 projected number of specimens. (Reprinted with permission of the Pan American Health Organization.)

Table 1 gives the annual numbers of confirmed cases of polio (from wild virus) for the time period, 1984–1996, for each of the 17 countries in the Americas which reported at least one such case during those years. The occurrence of some or no cases in calendar years allows us to consider the available data as a sequence of realizations of a dichotomous random variable. Of particular interest to us are the instances of first occurrences of cases after a string of years of fixed length, k, without any cases; that is, the realizations of the random variable, $\xi(t)$.

The empirical probabilities for key events, $\hat{P}\{N(t) > 0 \mid \xi(t) = k\}(k > 0)$, may be derived by straightforward adaptation of the available data. Focusing on properly defined strings of years, it is possible to count the number of strings where $\{N(t) > 0 \mid \xi(t) = k\}$, as proven by a later case, and compare that count to the sum of itself and the count of all other times when $\{\xi(t) = k\}$, and there was an opportunity to have observed a case (i.e., there is data for at least year $t + 1$ as well). Operationally, we typify all strings of year's data which contain zeroes. We say that a 'complete string' of consecutive years of data consists of a positive number of zeroes (years without cases, starting from the earliest zero in the string) followed by a positive number of cases as the final value in the string, defining its length. We say that an 'incomplete string' of consecutive years of data occurs whenever the string includes the year 1996 as its last year; thus making the string consist of zeroes alone, also defining its length. Note that each country in Table 1 has precisely one incomplete string. The empirical probability

$$\hat{P}\{N(t) > 0 \mid \xi(t) = k\} \quad (k > 0)$$

for a given country, as well as that for the region defined by all countries combined, is the quotient of the number of occurrences of 'complete strings' of at

Table 1
Confirmed poliomyelitis cases in the Americas: Annual totals by country, 1984–96 (Imported cases and cases due to vaccine omitted)

Country name	Year							
	1984	1985	1986	1987	1988	1989	1990	1991
Argentina	0	2	0	0	0	0	0	0
Bolivia	0	0	4	7	2	0	0	0
Brazil	82	461	612	236	106	2	0	0
Canada	1	1	0	0	0	0	0	0
Chile	0	0	0	1	0	0	0	0
Colombia	18	36	64	114	41	5	4	8
Dom. Rep.	0	2	2	0	1	0	0	0
Ecuador	0	0	20	10	9	2	1	0
El Salv.	19	10	23	54	12	0	0	0
Guatemala	6	29	33	22	38	0	3	0
Haiti	63	90	36	12	9	0	0	0
Honduras	76	4	6	15	6	0	0	0
Mexico	128	148	66	80	18	13	7	0
Paraguay	3	3	0	0	0	0	0	0
Peru	129	67	39	45	55	1	3	1
Suriname	1	0	0	0	0	0	0	0
Venezuela	9	8	27	45	20	1	0	0
Totals	542	866	935	646	317	24	18	9

N.B., there were no confirmed cases in the Americas in 1992, 1993, 1994, 1995 or 1996.

least length $k+1$ divided by the number of occurrences of any strings ('complete' or 'incomplete') of at least length $k+1$. It is seen that Table 1 has four complete strings of length $k+1=2$, two complete strings of length $k+1=3$ and one of length $k+1=4$. The 17 incomplete strings may be similarly counted. This yields the following empirical probabilities, $\hat{P}\{N(t)>0 \mid \xi(t)=k\}(k>0)$:

$$\hat{P}\{N(t)>0 \mid \xi(t)=1\}=\frac{7}{24}=0.292,$$

$$\hat{P}\{N(t)>0 \mid \xi(t)=2\}=\frac{3}{20}=0.150,$$

$$\hat{P}\{N(t)>0 \mid \xi(t)=3\}=\frac{1}{18}=0.056,$$

$$\hat{P}\{N(t)>0 \mid \xi(t)=k\}=0 \quad (k=4,5,\ldots,10).$$

It is not possible to tell from the data on Chile whether precisely three years or at least three years had elapsed before the confirmed case seen in 1987. We have made the former assumption (i.e., precisely three full years had passed without a reported case).

These data are consistent with the notion that a geometric model holds, whereby probabilities are halved with each passing year without cases.

No data on provinces or states are available prior to 1987. Without aggregating this information for examining data across countries, there could only be fragmentary investigations. Thus, we pool information on provinces for the time period 1988–1996 and from data aggregated at that level we identify complete and incomplete strings of years of case data to calculate the desired empirical probabilities, similarly to the country level data. There are some instances of missing province level data for this time period; Tables 2 and 3 summarize the available information. Table 2 gives the occurrences of confirmed cases of polio in provinces based on the time since the last previous occurrence of a confirmed case in that province.

It is seen that of the 58 instances where provinces were identified as having any confirmed cases in 1988–96, 28 were instances where the provinces had $k = 0$, another 19 were for instances where provinces had $k \geqslant 1$, another nine were for when provinces had $k \geqslant 2$ and two were for provinces with $k \geqslant 3$. These data are also consistent with a geometric model.

5.1. Compatible cases

The geometric model also holds for the worst case scenario in which all compatible cases are counted as being confirmed. Province level data are presented

Table 2
Annual counts of occasions in the years, 1988–96, when provinces in the Americas had at least one confirmed case by corresponding value for k, years since previous detected case in the same province (Re-emergence of polio after being undetected for k years)

Value(s) of k	Year				Totals	Totals for similar k
	1988	1989	1990	1991		
$k=0$	20	5	2	1	28	28
$k=1$	0	1	4	0	5	
$k>0$ [a]	11	3	0	0	14	
Totals						19
$k=2$	0	0	1	1	2	
$k>1$ [a]	0	1	6	0	7	
Totals						9
$k=3$	0	0	0	1	1	
$k>2$ [a]	0	0	0	1	1	
Totals						2
Grand Totals	31	10	13	4	58	58

[a] Denotes that the value of k cannot be exactly determined.
N.B., there were no confirmed cases in the Americas in 1992, 1993, 1994, 1995 or 1996.

Table 3
Annual counts of occasions in the years, 1988–91, when provinces in the Americas had at least one confirmed or compatible case by corresponding value of k, years since previous detected confirmed or compatible case in the same province, during the years up to the last confirmed case in the country of the province (Re-emergence of polio after being undetected for k years)

Value(s) of k	Year				Totals	Totals for similar k
	1988	1989	1990	1991		
$k=0$	38	32	5	1	76	76
$k=1$	0	1	4	0	5	
$k>0$ [b]	10	10	0	0	20	
Totals						25
$k=2$	0	1	1	1	3	
$k>1$ [b]	0	2	3	0	5	
Totals						8
$k=3$	0	0	0	1	1	
$k>2$ [b]	0	0	0	1	1	
Totals						2
Grand Totals	48	46	13	4	111	111

[b] Denotes that the value of k cannot be exactly determined.
N.B., there were no confirmed cases in the Americas in 1992, 1993, 1994, 1995 or 1996.

in Table 3, which summarizes the occurrences of either confirmed or compatible cases in provinces (for the years 1988 through 1991, the last year of a confirmed case) based on the smaller of either the time since the last compatible case in the province or the time since the last confirmed case in the country.

It is seen that of the 111 instances where provinces were identified as having any confirmed or compatible cases in 1988–1991, 76 were instances where the provinces had $k = 0$, another 25 were for instances where provinces had $k \geqslant 1$, another eight were for when provinces had $k \geqslant 2$ and two were for when provinces had $k \geqslant 3$. This year to year decline is consistent with a geometric model.

As a final note on compatible cases, during the years 1992–1994, there were 13 countries from which there were compatible cases, yet not once did a country have successive compatible cases separated by more than one calendar year.

The data in Tables 1–3 allow us to restate Eq. (12) with a single numerical (conservative) upper bound given to its right-hand side, the probability of persistence, that is consistent with historical data.

$$P\{N(t) > 0 \mid \xi(t) = k\} \leqslant \frac{1}{2}\left(P\{b < M(t-k+1) \leqslant B \mid \xi(t) = k\}\right)^k \leqslant \frac{1}{2}^{k+1}. \tag{16}$$

That is, with each further year of surveillance without cases, the chances of undetected wild poliovirus is further halved. It is noteworthy that in all instances where $k \geqslant 2$, the frequencies are at least halved for increasing k.

5.2. Incorporating surveillance level into the model

It is possible for surveillance efforts to expand consistently, but to have other forces (possibly unknown) temporarily cause the effective surveillance level to decrease. For a given year, t, let q_t, denote the effective surveillance level as a fraction of the level that would have been produced by the same efforts without the disruptive other forces. We may think of it as representing the chances that the exogenously caused decrease in effectiveness would cause a polio case that would otherwise be confirmed to be missed during a given year.

Theorem 2.

$$P\{N(t) > 0 \mid \xi(t) = k\} \leqslant \tfrac{1}{2}(q_t)^{-1}(P\{b < M(t-k+1) \leqslant B \mid \xi(t) = k\})^k, \tag{17}$$

where

$$P\{\xi(t) = 0 \mid N(t) > 0\}$$

is the effective surveillance level.

Proof. To show the effect of this refinement of the basic model on Eq. (12) we write

$$P\{\xi(t) = k \mid N(t) > 0 \text{ and } \xi(t-1) = k-1\} = [1 - xP\{N(t) > 0 \mid \xi(t) = k\}^{-1}]^{-1},$$

an identity obtained by applying Bayes' theorem, where

$$x = P\{\xi(t) = 0 \mid \xi(t-1) = k-1\}/P\{\xi(t) = k \mid \xi(t-1) = k-1\}.$$

Bayes' theorem is applied in such a way that there is no conditioning on the event

$$\{N(t) > 0\}.$$

Further, it is noted that

$$\{\xi(t) = k \text{ and } \xi(t-1) = k-1\} = \{\xi(t) = k\},$$

and terms are rearranged to obtain the identity. Then, taking the Taylor's series expansion for

$$P\{N(t) > 0 \mid \xi(t) = k\},$$

about 0 and rearranging terms we find that

$$P\{\xi(t) = 0 \mid N(t) > 0\},$$

is roughly proportional to the reciprocal of $P\{N(t) > 0 \mid \xi(t) = k\}$ and Eq. (12) becomes

$$P\{N(t) > 0 \mid \xi(t) = k\} \leqslant \tfrac{1}{2}(q_t)^{-1}(P\{b < M(t-k+1) \leqslant B \mid \xi(t) = k\})^k.$$

□

It is seen, thus, that incorporating level of surveillance into the model does not change the structure of Eq. (12). It can, however, have a substantial impact on the resultant upper bound for the probability of persistence.

5.3. Example

Let us assume that the same upper bound used on the right-hand side of Eq. (16) is appropriate for Eq. (17). Then

$$P\{N(t) > 0 \mid \xi(t) = k\} \leqslant \frac{1}{2}(q_t)^{-1}(P\{b < M(t-k+1) \leqslant B \mid \xi(t) = k\})^k$$
$$\leqslant (q_t)^{-1}\left(\frac{1}{2}\right)^{k+1}. \tag{18}$$

The national annual rate of AFP per 100 000 population <15 years of age is used as an indicator of the strength of a country's surveillance system: rates below 1/100 000 are considered to be indicative of surveillance failures. We give numerical estimates for q_t, the effective surveillance level, by relating it to the prevailing AFP rates. Consider the estimator of q_t defined by

$$\hat{q}_t = \min\left[1, \frac{\zeta_t}{\ddot{\zeta}}\right],$$

where ζ_t = AFP rate for year t and $\ddot{\zeta}$ = overall AFP rate for the Americas for year t.

Using, for illustration, data for Haiti for $t = 1991$, we have

$\zeta_{1991} = 0.63$ per 100 000 population under 15 years of age,

$\ddot{\zeta} = 1.10$ (rate for Americas, combined, per 100 000 under 15 years) and, thus,

$\hat{q}_{1991} = 0.573$.

Since $\xi(1991) = 3$ for Haiti, it follows from Eq. (18) that

$$P\{N(1991) > 0 \mid \xi(1991) = 3\} \leqslant (0.573)^{-1}\left(\frac{1}{2}\right)^4 = 0.109.$$

This refines the corresponding estimate from Eq. (16) of

$$P\{N(1991) > 0 \mid \xi(1991) = 3\} \leqslant \left(\frac{1}{2}\right)^4 = 0.0625.$$

In this way the model becomes directly responsive to changes in surveillance effectiveness.

6. Further remarks

A mathematical model has been presented which uses fluctuation theory to relate the time elapsed since the last detected case of paralytic poliomyelitis caused by wild poliovirus to the probability that the transmission of indigenous wild poliovirus has been stopped. The appropriateness of applying the model to various geographical regions was investigated using data about the occurrence of confirmed cases of polio since 1985, the time of the eradication initiative adopted by PAHO. Since the model is conservative, in that it gives upper bounds for the probability of persistence, its appropriateness vis-a-vis the data addressing countries with the most recent confirmed cases makes it appropriate for all countries in the Americas. The model seems to apply also to provinces and to the Americas as a whole, not entirely surprising since in the final stages of eradication, there would likely be only one province involved. It suggests that if four years have elapsed since the last reported confirmed case of paralytic poliomyelitis (caused by wild poliovirus), and no other confirmed cases have been identified, the probability of undetected indigenous wild poliovirus transmission is less than 5%.

There is retained a note of caution in light of mass migrations that have on occasion occurred (e.g., from Haiti and Cuba, most recently) which may bring about instability sufficient to violate modeling assumptions. It is noteworthy, however, that no cases of polio have been recently detected in countries from which those migrations originated, with no apparent weakening of the surveillance efforts. There is no concern about the ramifications of mass immunization (e.g., as have occurred in Brazil and Peru) on the model, because even though it 'jolts' the system being modeled, it does so in the direction of conservatism, thus making the true probability of persistence smaller and making even more valid an upper bound for it.

Because importations of wild poliovirus may occur from other regions of the world, surveillance of acute flaccid paralysis and wild poliovirus must be maintained in the Americas until global eradication has been achieved.

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