

# Status of Measles Elimination from the Reported Outbreaks: Fars Province, 2001–03

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## Abstract

**Background:** The status of measles elimination is best summarized by evaluation of the effective reproduction number  $R$ ; maintaining  $R < 1$  is necessary and sufficient to achieve elimination. In the present article, we estimated reproduction number  $R$  for the measles data reported for the Fars province of Iran in 2001–03.

**Methods:** We estimated  $R$  by using sizes and durations of chains of measles transmission and the proportion of cases imported, when offspring distribution is either Poisson or geometric. In each case, we calculated the profile 95% confidence intervals. These comprised 575 cases, forming 191 chains of transmission, of which 79 had  $> 1$  case. 128 cases were classified as importations.

**Results:** The results using the Poisson and geometric distribution for offspring and the proportion of cases imported differed slightly, but all 3 methods gave an  $R < 1$ . The results were not sensitive to the minimum size and duration of outbreak considered, as long as single-case chains were excluded, or to exclusion of chains without a known important source.

**Conclusion:** These results demonstrated that susceptibility to measles was beneath the epidemic threshold and that endemic transmission was eliminated.

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**Keywords •** Measles • outbreak • Iran

## Introduction

**D**uring 2001–03, in the Fars province, southern Iran, 575 patients with measles were reported. For 185 of these patients, a link to importation could not be identified. Thus, the question raised as if the goal of measles elimination has been achieved or not. For elimination to be achieved, there must be no sustained chains of endemic transmission; that is, all cases must be linked to an importation. However, even the most robust surveillance system cannot detect every such link. Thus, a method of assessing elimination based on the surveillance data which does not require that the system detects all links to importation is an essential tool.<sup>1</sup> Because zero measles incidence cannot be sustained in the presence of imported disease (and cases will continue to be imported until the disease is eradicated globally), DeSerres, et al,<sup>1</sup> have previously proposed that elimination be defined as “a

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situation in which endemic transmission has stopped, sustained transmission cannot occur, and secondary spread from importations will end naturally, without intervention".<sup>3</sup> This definition is equivalent to a requirement to maintain the effective reproduction number of measles ( $R$ ) below the threshold of  $R=1$ .<sup>3,4</sup> Using the methods of proportion of cases imported, outbreak size and outbreak duration,<sup>1,5-8</sup> we analyzed the surveillance data on measles in Fars province from 2001–03.

## Methods

### *Confirmed cases of measles in 2001–03*

Confirmed cases of measles were reported to the Center for Disease Control and Prevention of Fars province with accompanying epidemiologic information. We classified the importation status of cases and groups them into chains of transmission based on either known links found during the investigations or close temporal and geographical clustering.

### *Calculation of $R$ from measles case data*

When endemic transmission of measles has stopped, imported cases drive the observed epidemiology. Some importations will produce no secondary cases, whereas others will cause some limited spread to susceptible persons. The extent of this spread depends on the effective reproduction number ( $R$ ), the average number of secondary cases produced by each case. When  $R < 1$ , this spread always be limited and endemic transmission cannot become re-established.

When endemic transmission has been interrupted, data on measles cases may be used to estimate the value of  $R$  by three methods: from the proportion of cases imported ( $R=1$ –proportion of cases imported); from the distribution of sizes of chains of transmission; and from the distribution of duration of chains of transmission.<sup>2</sup>

To estimate the  $R$  by these methods, one must assume that all chains of transmission are finite. If this assumption is made, the estimates of  $R$  obtained with these methods will always be  $< 1$ —although the upper limit of the confidence interval of  $R$  may  $> 1$ . If the methods are inappropriately applied to data from a period when endemic transmission occurred (but was reported as a series of separate chains because of undetected links in the chain of transmission), the value of  $R$  obtained would be marginally  $< 1$ , but the confidence interval of  $R$  would be expected to include one, hence, not excluding the probability of endemic transmission.

The first method requires a conservative definition of "importation," otherwise,  $R$  may be

underestimated. Therefore, we considered as an importation any persons who traveled outside the Fars province during 18 days before the onset of rashes, unless the onset occurred  $\geq 7$  days after the onset of rashes in a traveling companion.

For example, if a family returned from a holiday outside the Fars province, and one member developed measles five days after returning and another developed measles 15 days after returning, we considered the first one as importation and the second one as spread from this importation. Our definition is more conservative than the definition provided by the National Immunization Program, which would consider both of these cases importation, solely on the basis of the time between the travel and the disease onset for each individual.

For the other two methods of estimating  $R$ , a "chain of transmission" or "chain" is defined as the entire series of cases that can be linked to the same source. This includes single-case chains, which are not linked to any other cases. We calculated the duration of a chain of transmission as the difference between the states of the disease onset of the first and the last cases. If this difference was less than six days, cases were considered as being in the same generation; the difference from 7–14 days was considered as one generation of spread; 15–24 days was considered as two generations; and one generation was added for every extra 10 days observed in the difference.

These methods of estimating  $R$  are based on a model of the spread of infection that predicts the distribution of sizes and durations of chains of transmission that arise from an importation. The model assumes that the number of secondary cases caused by a single infectious individual has a Poisson distribution with a mean of  $R$ , or a geometric distribution with a mean of  $R = (1 - p)/p$  where  $p$  is the probability of success in the geometric distribution.

For a given population the three estimates of  $R$  (and their associated 95% confidence intervals) are best obtained by analysis of the data using the maximum likelihood approach (Appendix).

An important methodological consideration is that the minimum size and duration of chains that should be considered in these analyses. Smaller chains, especially single-case chains, are less likely to be detected by surveillance but more likely to be composed of false-positive cases. Discarding chains of transmission below a minimum size or duration may reduce the bias originates from these factors but has the disadvantage of reducing the data available for the analysis. To reduce the bias but retain sufficient data, we arbitrarily based our analysis of chain size on those involving

$\geq 2$  cases and our analysis of chain duration on those with at least one generation of secondary spread. We investigated the sensitivity of our results to the minimum size and duration considered by estimating  $R$  for the minimum chain sizes of 1–5 cases and the minimum chain duration from zero to four generations of spread.

Chains of transmission with no identified source present another challenge for the analysis. One possibility is to adjust the data by adding missing cases. However, for each chain with no identified source, there are three possible explanations: It may be linked to an unidentified importation; it may have an unidentified link to another identified chain; or, especially for single-case chains, it may be the result of a false-positive laboratory test. The appropriate adjustment would require adding an imported case, adding an indigenous case, and deleting the chain, respectively. Because it is not known which of these possibilities applies to each chain, it is not possible to adjust the data in this way. In the sensitivity analysis for the minimum chain size and duration, we conducted all the analyses twice—by including and excluding chains without an identified imported source. For estimation of  $R$  by methods of distribution of chain size and chain duration, we

obtained the likelihood function and maximize it numerically using the software Maple 7.

## Results

### Importation status

During 2001–03, 575 confirmed cases of measles were reported to the Center for Disease Control and Prevention of Fars province. Those included 249 cases in 2001, 211 in 2002, and 115 cases in 2003. Of these cases, we considered 54, 39, and 35 as importations (table 1). The proportions of imported cases were 22%, 18%, and 30% in 2001, 2002, and 2003, respectively, given an overall proportion of 22% over the three years.

### Data on chains of transmission of measles

During the three years, cases of measles were reported from a total of 191 chains of transmission (table 1), 112 of which were single-case chains. Of the single-case chains, 75 were imported and 37 could not be linked to importation. There were 79 chains of transmission with  $> 1$  case, 61 of which had at least three cases and only eight had  $\geq 10$  cases (table 1). Of the 79 chains with  $> 1$  case, 42 had  $\geq 2$  generations of spread; only 18 of these chains had  $\geq 5$  generations of spread (table 2).

**Table 1:** Number of chains of measles transmission of each size, by identified link to importation, Fars province, 2001–03.

2001–03		2003		2002		2001		Number of cases in chain
Not linked	linked							
37	75	12	23	13	22	12	30	1
5	13	1	3	1	2	3	8	2
2	10	1	2	0	3	1	5	3
5	10	0	2	3	4	2	4	4
6	3	1	0	2	3	3	0	5
2	6	0	3	2	2	0	1	6
1	1	1	0	0	0	0	1	7
2	2	1	1	1	0	0	1	8
1	2	0	1	0	1	1	0	9
0	1	0	0	0	0	0	1	12
1	1	0	0	0	1	1	0	15
0	1	0	0	0	0	0	1	18
1	1	0	0	1	0	0	1	23
0	2	0	0	0	1	0	1	29
63	128	17	35	23	39	23	54	Total no. of chains
185	390	37	78	80	131	68	181	Total no. of cases

**Table 2:** Number of chains of measles transmission of each duration (in generations) for the 79 chains involving  $>1$  case, by identified link to importation, Fars province, 2001–03.

2001–2003		2003		2002		2001		Generation of spread
Not linked	Linked							
4	4	1	0	1	1	2	3	0
9	21	3	5	3	5	3	11	1
4	9	2	2	1	3	1	4	2
3	3	1	0	1	1	1	2	3
1	4	1	1	0	1	0	2	4
2	1	1	0	0	1	1	0	5
2	2	0	1	1	0	1	1	6
1	2	0	1	0	0	1	1	8
0	2	0	0	0	1	0	1	9
0	2	0	1	0	0	0	1	10
0	3	0	1	0	1	0	1	13
26	53	9	12	7	14	10	27	Total

For eight chains, the interval between the first and the last case was < 7 days, so cases were categorized in the same generation (i.e., no spread); four of these chains were linked to an imported case, and another for chains not linked to an imported case. There were 71 durations available (table 3).

### Estimates of $R$

Table 4 shows the estimated values of  $R$  for measles in Fars province during 2001–03, assuming a Poisson distribution of offspring derived from three methods. Table 5 also shows the estimates assuming a geometric distribution of offspring derived three methods. In each case, the estimates are <1 and did not change significantly as calculated by either of the methods. Furthermore, the profile 95% confidence intervals of  $R$  were calculated.

Sensitivity analyses showed that the estimates of the reproduction number ( $R$ ) were considerably lower if single-case chains were included in the analysis based on size, and if the chains with no spread were included in the analysis based on the duration; however, they were otherwise fairly consistent (tables 6 and 7). Estimates of  $R$  did not change significantly when the analysis was limited to the chains with an identified imported source; however, the confidence intervals of  $R$  became wide.

### Discussion

Our analyses suggested that during 2001–03,

**Table 6:** Sensitivity analyses for the minimum chain size used to estimate the reproduction number ( $R$ ) for measles in Fars province for all chains and for only chains with an identified link to importation, 2001–03.

Estimate of $R$ (95% confidence interval)		
Minimum Chain size Considered	All chains	Chains with an identified imported Source only
1	0.40 (0.35, 0.46)	0.72 (0.62, 0.81)
2	0.73 (0.68, 0.770)	0.77 (0.67, 0.88)
3	0.72 (0.63, 0.81)	0.81 (0.70, 0.93)
4	0.79 (0.70, 0.89)	0.84 (0.72, 0.98)
5	0.77 (0.72, 0.96)	0.86 (0.74, 1)

**Table 7:** Sensitivity analyses for the minimum number of generations of spread used to estimate the reproduction number ( $R$ ) for measles in Fars province for all chains and for chains with an identified link to importation, 2001–03.

Estimate of $R$ (95% confidence interval)		
Minimum generations of spread Considered	All chains	Chains with an identified imported Source only
0	0.71 (0.66, 0.79)	0.72 (0.62, 0.81)
1	0.79 (0.70, 0.89)	0.82 (0.72, 0.93)
2	0.84 (0.73, 0.99)	0.87 (0.75, 0.99)
3	0.85 (0.72, 0.98)	0.88 (0.75, 1)
4	0.84 (0.70, 0.99)	0.84 (0.72, 1)

the estimated  $R$  is <1. These results demonstrated that in Fars province, susceptibility to measles is lower the epidemic threshold and that endemic transmission has been eliminated. Furthermore, the values of  $R$  were in the range of 0.68–0.81, using the three methods of

**Table 3:** Durations (days) of 71 measles outbreaks with secondary spread.

Duration	8	9	11	13	14	17	19	21	24	27	30	33
Frequency	3	8	9	6	4	6	4	2	1	3	1	2
Duration	36	37	41	46	49	53	56	59	61	64	76	79
frequency	2	2	1	1	1	1	1	1	1	1	1	1
Duration	82	87	91	97	102	127	129	133				
Frequency	1	1	1	1	1	1	1	1				

**Table 4:** The reproduction number ( $R$ ), assuming a Poisson distribution of offspring, for measles in Fars province, as derived by three estimation methods.

Estimation method	Estimate of $R$ (95% confidence interval)			
	2001	2002	2003	2001-2003
Proportion of cases imported	0.78 (0.67-0/89)	0.82 (0.70-0.95)	0.69 (0.54-0.85)	0.78 (0.70-0.86)
Distribution of chain size	0.73 (0.61-0.87)	0.75 (0.62-0.89)	0.66 (0.48-0.87)	0.73 (0.65-0.81)
Distribution of chain duration	0.79 (0.66-0.93)	0.77 (0.59-0.97)	0.80 (0.58-0.97)	0.78 (0.70-0.86)

**Table 5:** The reproduction number  $R$ , assuming a geometric distribution of offspring, for measles in Fars province, as derived by three estimation methods.

Estimation method	Estimate of $R$ (95% confidence interval)			
	2001	2002	2003	2001-2003
Proportion of cases imported	0.78 (0.63-0/88)	0.82 (0.71-0.95)	0.69 (0.60-0.79)	0.78 (0.72-0.84)
Distribution of chain size	0.68 (0.54-0.85)	0.70 (0.56-0.89)	0.60 (0.41-0.86)	0.68 (0.58-0.78)
Distribution of chain duration	0.81(0.67-0.95)	0.79(0.61-0.99)	0.82(0.66-0.90)	0.81 (0.72-0.90)

proportion of cases imported, chain size and chain duration and assuming either offspring distribution of Poisson or geometric. This value is approaching one, suggesting a need for control of measles in Fars province.

The estimated  $R$  derived from the proportion of imported cases, was higher than that derived from the distribution of chain size and was less than or equal to that obtained from the distribution of chain duration. However, the three estimates are almost the same. The estimated  $R$  in the proportion of imported method depended only on the number of linked chains and number of cases, but those derived in two other methods depended on the number of linked chains, number of cases and number of outbreaks with generations.

The estimates were also robust to re-analyze the subsets of the data, varying with the minimum size chain considered (as long as single-case chains were excluded) and varying with the minimum duration (as long as chains with zero generations of spread were excluded). Considering only chains with an identified imported source also produced larger estimates of  $R$  but widened the confidence intervals. For our base analysis, the distributions of chain size and duration did not differ significantly.

In the elimination phase of a disease control programme, surveillance system should be capable of detecting any impending failures of the elimination strategy, failures to implement this strategy correctly, or foci of transmission in which additional measures may be needed. Active search for every isolated cases gives little if any benefits, because only large clusters of cases would provide evidence of the ineffectiveness of the programme. As a minimum, surveillance should determine whether each reported case has been imported, to enable a single estimate of  $R$  to be made. To avoid underestimating  $R$  by use of this method, it is important that the proportion of cases imported is not overestimated. In this respect, the definition of the Center for Disease Control and Prevention of an imported case was not appropriate for our analysis, and it was therefore necessary to reclassify some cases.

Estimating  $R$  from the distribution of chain size and duration is beyond the "minimum" requirements mentioned above. To permit such analyses, surveillance must emphasize linking cases into chains of transmission. In practice, some links between cases will not be identified, even for diseases that always induce medical consultation. Therefore, it is reasonable to assume that cases of measles occurring in temporal and geographic clusters are part of the same chain.

Clear communication of goals and achievements to the public, the media, and politicians is an important aspect of a disease control programme. Whatever definition of elimination is adopted by epidemiologists and public health professionals, in the public mind, the word "elimination" will imply the absence of cases. Use of the expression "elimination of endemic measles transmission" rather than "elimination of measles" may help to inform the public that measles cases still occur.

*Appendix*

We assumed a Poisson or geometric distribution for the number of secondary cases produced by an infected individual, with a mean of  $R$ , and we assumed that this did not change during the course of a chain of transmission. With these assumptions, we derived the log likelihood function (L) for each method of estimating  $R$ . The best estimate of  $R$  is the value that maximizes the log likelihood. Approximate 95% confidence intervals can be obtained from the profile log likelihood as the range of values of  $R$ .

*Proportion of cases imported*

The log likelihood of I imported cases generating a total of C cases is given by.<sup>2</sup>

$$L(R) = (C - I) \log R - CR + \text{constant}$$

*Distribution of chain size*

Following a single importation, the probability,  $S_j$ , of a chain with j cases (including the initial importation) for a Poisson distribution is given by.<sup>9-12</sup>

$$S_j = \frac{R^{j-1} e^{-Rj} j^{j-2}}{(j-1)!}, \quad j = 1, 2, \mathbf{L}$$

Or, the probability,  $S_j$ , of a chain with j cases (including the initial importation) for a geometric distribution for offspring is given by.<sup>9-12</sup>

$$S_j = \frac{1}{2j-1} \binom{2j-1}{j-1} \frac{R^{j-1}}{(1-R)^{2j-1}} \quad j = 1, 2, \mathbf{L}$$

If  $m_j$  is the observed number of chains with j cases, and only chains with at least j cases are considered, the log likelihood is then given by.<sup>1</sup>

$$L(R) = \sum_{j=1}^{\infty} m_j \log S_j - \log \left( 1 - \sum_{j=1}^{l-1} S_j \right) \sum_j^{\infty} m_j$$

*Distribution of chains duration*

The probability of a chain with at most  $k$  generations of secondary spread,  $f_k$ , assuming a Poisson distribution for offspring is given by

$$f_k = e^{-R} E_k(e^{Re^{-R}}), \quad k = 0,1,2,\mathbf{L}$$

Where  $E_k(x)$  denotes the iterated exponential function (the number  $x$  to the power of  $x$ ,  $k$  times, so that  $E_0(x) = 1$ ,  $E_1(x) = x$ ,  $E_2(x) = x^x$ , etc),<sup>6</sup>; assuming a geometric distribution for offspring

$$f_k = \frac{1 - R^{k+1}}{1 - R^{k+2}} \quad k = 0,1,2,\mathbf{L}$$

If  $n_k$  is the observed number of chains with  $k$  generations of spread, and only chains with at least  $b$  generations of spread are considered, the log likelihood  $L$  is given by.<sup>1</sup>

$$L(R) = \sum_{k=b}^{\infty} n_k [\log(f_k - f_{k-1}) - \log(1 - f_{b-1})]$$

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