

Waning immunity is associated with periodic large outbreaks of mumps: a mathematical modelling study of Scottish data

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Provisional

Waning immunity is associated with periodic large outbreaks of mumps: a mathematical modelling study of Scottish data

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7 **Keywords: Mumps, vaccination, waning immunity, mathematical and computational modelling**
8 **and simulation, Bio-PEPA**

9 **Abstract**

10 Vaccination programs for childhood diseases, such as measles, mumps and rubella have greatly
11 contributed to decreasing the incidence and impact of those diseases. Nonetheless, despite long
12 vaccination programmes across the world, mumps has not yet been eradicated in those countries:
13 indeed, large outbreaks continue. For example, in Scotland large outbreaks occurred in 2004, 2005
14 and 2015, despite introducing the MMR (Measles- Mumps- Rubella) vaccine more than twenty years
15 ago. There are indications that this vaccine-preventable disease is re-emerging in highly vaccinated
16 populations. Here we investigate whether the resurgence of mumps is due to waning immunity, and
17 further, could a booster dose be the solution to eradicate mumps or would it just extend the period of
18 waning immunity? Using mathematical modelling we enhance a seasonally-structured disease model
19 with four scenarios: no vaccination, vaccinated individuals protected for life, vaccinated individuals
20 at risk of waning immunity, and introduction of measures to increase immunity (a third dose, or a
21 better vaccine). The model is parameterised from observed clinical data in Scotland 2004-2015 and
22 the literature. The results of the four scenarios are compared with observed clinical data 2004-2016.

23 While the force of infection is relatively sensitive to the duration of immunity and the number of
24 boosters undertaken, we conclude that periodic large outbreaks of mumps will be sustained for all
25 except the second scenario. This suggests that the current protocol of two vaccinations is optimal in
26 the sense that while there are periodic large outbreaks, the severity of cases in vaccinated individuals
27 is less than in unvaccinated individuals, and the size of the outbreaks does not decrease sufficiently
28 with a third booster to make economic sense. This recommendation relies on continuous efforts to
29 maintain high levels of vaccination uptake.

30 **1 Introduction**

31 To prevent, control and eradicate childhood diseases, vaccination programs have been adopted
32 throughout the world. For example the trivalent measles-mumps-rubella vaccine (MMR) [1, 2, 3] has
33 been highly successful for both measles and rubella reduction in many countries. Despite near
34 eradication of both measles and rubella [4,5,6], elimination of mumps has not been achieved and
35 could be considered to be re-emerging, despite initial early success in reducing mumps cases. In the

36 last decade, many countries such as Belgium [7], Korea [8], the Netherlands [9] and the US [10] have
37 reported a dramatic increase in the incidence of mumps. In Scotland, 2004/2005 saw a sudden high
38 resurgence in mumps with approximately 4500 cases, eight years after the second dose of MMR was
39 included in the vaccination program (which was predicted to substantially reduce mumps outbreaks
40 [11]). One hypothesis is that the resurgence was related to declining vaccine coverage [12, 13], in
41 particular, a widespread scare related to autism which led to some parents refusing to vaccinate their
42 children. This can be easily debunked: the herd immunity threshold is estimated at 75-86% [14] and
43 mumps vaccination levels have stayed above that level (e.g. in Scotland, ranging from 87% to 94%
44 pre-2004). In addition Donaghy et al [14] argues that those infected during the 2004/2005 epidemics
45 are characterised by low uptake of a single dose of MMR (catch-up campaign) and being of school
46 age at time when the mumps virus had greatly reduced circulation in that group, delaying infection.
47 The study undertaken by DeStefano et al [15] analysing the number of antigens in both children with
48 and without autism, shows that there is no association between receiving vaccine and developing
49 autism.

50 A second hypothesis is to link vaccination status and age, e.g. proposing that outbreaks continue in
51 the older population but die out in the increasingly vaccinated population. However, while age
52 structure has shown to be informative in many models of traditionally childhood diseases [16, 17, 18,
53 19], current studies suggest that age is not the key determinant in mumps. Snijders et al. [20] do not
54 find any significant interaction between these two features. In addition, several studies of different
55 outbreaks occurring at different times and locations in the US and Canada [21] indicate that there is
56 no evidence that age is the main factor leading to mumps spread. For instance, the outbreaks
57 occurring in New York (Sullivan, Brooklyn, Rockland county and Orange county), New Jersey and
58 Canada show variable average of infected age groups (Sullivan: 12 years, Brooklyn: 14 years,
59 Rockland county: 12 years, Orange county: 18 years, New Jersey: 19.5 years and Canada: 27.5).
60 However, it was confirmed that all cited cases were related to religious events or camping in
61 Sullivan, with the majority fully vaccinated. It was also reported that the series of outbreaks were due
62 to one fully vaccinated child aged 11 years who had been infected during his travel to UK. Snidjer et
63 al. [20] analysed a group of infected whose ages ranged in 3 to 13 years. The authors find out that no
64 significant difference between the attack rate of the group aged 10-13 years and 3-5 years.
65 Considering Scotland specifically, Donaghy et al. [14] argued that the shift of ages observed in the
66 epidemic in Scotland suggests that the propagation of mumps is becoming more widespread and
67 diverse as the targeted population becomes more dynamic and mobile.

68 Having rejected the first two hypotheses, the arguments used lead to the third and more plausible
69 hypothesis: MMR vaccine efficacy against mumps reduces over time [13]. In 2015 67% of those
70 infected in Scotland were fully vaccinated individuals (1 and 2 doses confounded). Moreover, most
71 primary cases occurred in adolescent and young adults, in contrast to the pre-vaccine era where
72 outbreaks were among children of primary school age. Similar patterns can be found for Belgium in
73 2012 [7] and in the US in 2006 [10]. Serological studies [8, 22] show that susceptibility level
74 increases (immunity wanes) as time from vaccination increases; however, the antibody threshold
75 defining the protective level is not well specified for mumps [23]. Even using two doses of the MMR
76 vaccine, existing analyses [8, 24] stress that some of the population will remain at risk of disease
77 unless additional control strategies are adopted.

78 We investigate the hypothesis of waning immunity using mathematically-based computational
79 modelling. The basic model is a seasonal compartmental SEIR model [25, 26, 27], to which
80 vaccination and immunity is added. We first show that the model produces comparable results to
81 observed mumps data in Scotland [28], matching endemic levels of mumps with occasional larger

82 epidemics, as in 2005 and 2015. Having established the accuracy of the model with historical data,
83 we use it predictively to better understand the relationship between immunity and transmission, to
84 illuminate long-term patterns of resurgent outbreaks, and to determine whether these can be
85 controlled by extending immunity duration (e.g. by using another booster). While modelling has been
86 previously used to investigate mumps and vaccination [7, 27, 29], the novelty of our approach lies in
87 consideration of waning immunity and associated optimal control strategies. Our model shows
88 clearly that waning immunity is a driver for a long period of oscillating outbreaks. Moreover, by
89 working with epidemiologists to use mathematics to understand the observed clinical data, we
90 illustrate the power of mathematics to inform public health policy through multi-disciplinary
91 collaboration.

92 **2 Mumps epidemiology in Scotland**

93 During the period 1988-2015, Health Protection Scotland (HPS), the national surveillance centre for
94 Scotland, reported 10943 mumps cases. 10486 of these cases were between 2004 and 2015.
95 Vaccination was introduced in 1988, with a second dose introduced in 1996. Fig. 1 shows the
96 epidemic curve of mumps, and the vaccination uptake curves for both vaccines (MMR1 and MMR2).
97 Observe the initial success of the vaccine (1988-2003) contrasted with a long potential cycle from
98 2004-2015, possible with sub-cycles (2005-2009, 2009-2012, 2012-2015). The 2004/2005 outbreak
99 was related only partly to the decrease in vaccination coverage shown in Fig. 1 [14]. The majority of
100 cases (94%) were born before 1990 (aged 15+ years), with only a few of them receiving only one
101 dose of MMR (around 1%) or none at all. Similarly for the outbreaks in 2009 and 2012. In 2015 the
102 highest incidence of mumps (63%) was related to the group born 1991-2000 (aged 15-24 years).
103 Cameron and Smith-Palmer [24] argue that the 2015 outbreak was the first where the majority of
104 cases were fully vaccinated. Transmission is a complex feature to model as it can be influenced by
105 many factors (vaccination history, current immunity status, age, opportunity for social mixing,
106 geography, and so on). Moreover, some of these factors are confounded (e.g. age and vaccination
107 history). We propose in this model that vaccination history is used as a proxy for these combined
108 effects. Therefore, the main question arising is: why are vaccinated individuals being infected? Here
109 we focus on the long curve (2005-2015) relating to the long inter-epidemic period. We explore these
110 features within the model presented in Section 3, using the Bio-PEPA plugin tool [30] and
111 deterministic simulation to provide time series prediction of the number of infected individuals. The
112 model is parameterised and validated on data up to 2015, and then to further validate its predictive
113 performance it is shown to match 2016 data provided by HPS. The advantages for using the Bio-
114 PEPA formalism (a mathematically-defined computational modelling approach called process
115 algebra) have been fully argued in many works [30, 31, 32]. Here, the advantages are: formal
116 structuring of interactions between components, a compositional approach to building the
117 epidemiological model, and a range of analysis techniques to support the modeller in understanding
118 the system. The underlying semantics of Bio-PEPA is a continuous time Markov chain.

119 **3 Methods**

120 **3.1 Model structure, epidemiological assumptions and parameter estimates**

121 We consider a compartmental structure for a model of mumps formulated as an extended SEIR [11]
122 model including seasonality and waning immunity: natively susceptible (S1), vaccinated individuals
123 with MMR1 only (V1), vaccinated individuals with both MMR1 and MMR2 (V2), modified
124 susceptible who are vaccinated individuals who have become susceptible (S2), exposed individuals

125 (E), infected individuals (I) and recovered individuals who are regarded as immune for life (R) [11,
126 33]. Fig. 2 shows how these compartments interact.

127 Our goal is to provide as simple a model as is necessary to demonstrate the impact of waning
128 immunity, therefore we have ignored features which others have chosen to include. For example, the
129 models of Glass and Grenfell [34] and Barbarossa and Röst [35] include immunity levels and
130 immune-boosting through vaccination and interactions with infected. Since we have no data on
131 antibody levels as individuals interact we choose not to include this, choosing the simpler scenario
132 which can be parameterised through observed data. Neither do we include age-structure, as mumps
133 has ceased to be a mainly childhood disease. As shown in several works [14, 36, 37, 38], the range of
134 those infected with mumps has become more diverse due to a more mobile susceptible population.
135 Therefore, rather than stratifying the population by age, we assume a more homogeneously-mixed
136 population, with routine vaccination, and transmission based on seasonality and immunity status.

137 This model is general and could be parameterised for any seasonal disease with up to two
138 vaccinations. We use data from Health Protection Scotland (HPS) from 2004-2016 [28] and some
139 parameters from the literature [11, 39]. These are detailed in Table 1, with some explanatory text.

140 • Demographic estimation

141 Birth and death rate estimated from Scottish demographic data [28].

142 • Immigration rate estimation

143 As the net migration to Scotland is insignificant (typically 15,000 per year), the model has been
144 simplified by having neither mass emigration nor immigration of susceptible individuals. A small
145 constant rate of immigration of infected individuals is required to prevent the disease dying out
146 entirely. This is justified by the knowledge that there is immigration, and there are many populations
147 in the world where mumps is more prevalent and the global population is more mobile, transmitting
148 disease between countries. A small rate of immigration of infectious individuals is estimated as in
149 Finkenstadt et al [40] and Benkirane et al [31].

150 • Vaccination rates estimation (μ_2, μ_3)

151 According to vaccination data [41], our basic assumption is an average of 94% MMR1 vaccination
152 coverage (1988-2016) for children aged 0 to 2 years and 90% MMR2 vaccination coverage (1996-
153 2016) for children aged 3 to 5 years. According to past vaccination history [42, 43], we estimate the
154 susceptible portion of the remaining unvaccinated population at 20%. Within that proportion of
155 susceptible we consider 11% of those to be aged ten years or over according to current demographics.
156 It would be more realistic to consider a varying vaccination rate each year; however, we did not want
157 this to confound the patterns obtained through simply waning immunity. We do investigate scenarios
158 in which these average vaccination rates are varied across the simulation period, to show how this
159 affects the pattern of outbreaks.

160 • Waning immunity estimation (τ, δ)

161 Our basic assumption is individuals vaccinated with MMR1 and MMR2 (resp. only MMR1) are
162 temporarily protected and that immunity wanes towards susceptibility at constant rate δ (resp. τ).
163 Lebaron et al [23] report low antibody levels 4-9 years after MMR1 only, and 7-12 years after
164 MMR2 administration. We also investigate scenarios in which these rates are varied.

- 165 • Transmission rate estimation ($\beta_1, \beta_2, \beta_3$)

166 In our model, the transmission rate depends on two features: seasonality (High, Low) and type of
 167 susceptible (native susceptible, modified susceptible) giving four rates: β_1 (High season and native
 168 susceptible), β_2 (high season and modified susceptible), β_3 (low season and native susceptible), β_4
 169 (low season and modified susceptible). For seasonality, data report higher number of cases October
 170 to May, and fewer between June and September [28]. As most cases occurs in 17-24 year-olds this
 171 seasonality is further supported through an assumption that many of that group are likely to be in
 172 full-time education, and mixing more in semester-time than in the holiday. As the total number of
 173 infected at low season is small we assume $\beta_3 = \beta_4$. In addition, we assume $\beta_2 > \beta_1$ (transmission in
 174 modified susceptible is higher than in native susceptible). This follows from the model of Scherer
 175 and McLean [45], and is supported by the report of Cameron [44] that within 205 confirmed cases
 176 related to two health boards, 137 (67%) individuals were fully vaccinated. As transmission rate is
 177 based on the basic reproduction number R_0 (see Table 1), a range of proposed values were collected
 178 from literature [11, 13, 27], where R_0 is ranged [4-11]. See section 5 for sensitivity analysis of the
 179 particular choices of these rates.

- 180 • Incubation rate α and recovery rate γ

181 Established empirical studies [11, 27] estimate the incubation period between 12-25 days and the
 182 infectious period between 7-9 days [27]. For modelling convenience, we assume the same period of
 183 infection and incubation [43] for both natively susceptible and modified susceptible.

- 184 • Initial conditions

185 The initial mix of susceptible, vaccinated, exposed, infected and recovered is calculated for 1996
 186 according to the above assumptions about population based on vaccination beginning in 1988. See
 187 appendix 1 (model component).

188 The description of the model and parameters above can be summarised by seven ordinary differential
 189 equations:

$$190 \quad \frac{dS_1}{dt} = \mu_1 * N - \frac{\beta(t)S_1I}{N} - \mu S_1$$

$$191 \quad \frac{dV_1}{dt} = \mu_2 * N - \tau V_1 - \mu V_1$$

$$192 \quad \frac{dV_2}{dt} = \mu_3 * N - \delta V_2 - \mu V_2$$

$$193 \quad \frac{dS_2}{dt} = \delta V_2 + \tau V_1 - \frac{\hat{\beta}(t)S_2I}{N} - \mu S_2$$

$$194 \quad \frac{dE}{dt} = \frac{\beta(t)S_1I}{N} + \frac{\hat{\beta}(t)S_2I}{N} - \alpha E - \mu E$$

$$195 \quad \frac{dI}{dt} = \alpha E - \gamma I - \mu I + IMM$$

$$196 \quad \frac{dR}{dt} = \gamma I - \mu R$$

197 Where:
$$\beta(t)\{\text{resp. } \hat{\beta}(t)\} = \begin{cases} \beta_1 \{\text{resp. } \beta_2(t)\} & \text{if Time} \in [\text{October} - \text{May}] \\ \beta_3 & \text{if Time} \in [\text{June} - \text{September}] \end{cases}$$

198 This model is coded in Bio-PEPA (see Appendix 1). Analysis of the model is performed through
199 deterministic simulation. Stochastic simulation was used to guide model development but does not
200 provide additional information when identifying long term trends.

201 3.2 Model scenarios

202 To capture the impact of vaccination efficacy and the effect of waning immunity on the population of
203 Scotland for future projection of epidemics, the history of mumps epidemics (from pre-vaccine to
204 post-vaccine era) are reproduced where four strategies are considered:

- 205 • *Scenario one.* No vaccination. This is equivalent to the pre-vaccine era and useful for model
206 validation where the whole population is considered susceptible.
- 207 • *Scenario two.* Immunity does not wane: τ and δ are zero. This case reflects the introduction of a
208 vaccination protocol to case one, where immunity is assumed to be for life. This is consistent
209 with the period immediately following the introduction of vaccination.
- 210 • *Scenario three.* Immunity wanes in vaccinated individuals according to the assumptions above.
211 This scenario reflects modern reality, where mumps is resurgent. Our model is extended to two
212 separate but correlated models: the first model expresses unvaccinated individuals and the
213 second model expresses vaccinated individuals for whom immunity wanes. Scenario three is an
214 extension to case two by introducing the terminology of waning immunity.
- 215 • *Scenario four.* An additional medical intervention increases immunity duration. We explore
216 immunity duration across a range (10 to 80 years). This case is a particular variation of case
217 three, where the immunity duration is specified in the defined range. This scenario is to
218 predictively investigate possible future interventions.

219 4 Results

220 According to observed mumps data in Scotland in Fig. 1, and in conjunction with observed mumps
221 data in England and Wales in Fig. 9 (a and b) (see Appendix 3), three different periods of an
222 epidemiological shift in incidence are observed: pre-vaccine, successful post-vaccine and waning
223 immunity period. Fig. 3 depicts time series results for infected cases under scenarios 1-3. Overall, it
224 is clear that mumps occurs every year, regardless of vaccination or waning immunity; however, those
225 factors control the amplitude of the epidemic and the frequency of the highest peaks driving a long
226 term damping oscillation of large outbreaks. After 100 years the difference between the high and low
227 of the cycle is around 25 cases.

228 *Scenario One (no vaccination = pre-vaccine era)*

229 We begin by checking model performance without vaccine. Fig. 3 (a) shows an inter-epidemic period
230 of three years within an oscillatory pattern of mumps cases. This matches parameter values of
231 incubation period of 13 days, infectious period of seven days and a mean age of infection of five
232 years (all within the ranges of Table 1). This is supported by the incidence of mumps in England and
233 Wales [27] and observations in the literature reporting cycles of 2-5 years [29, 46].

234

235 We point out that predicted cycles do not damp out during 100 years of simulations. By varying
 236 seasonality parameter of the model, including removing seasonality altogether, we observed that after
 237 a long period the model reaches an endemic state. To further reinforce the suitability of the model we
 238 considered R_0 ranging from [7 - 14]. Fig. 4 (see Appendix 3) shows that increasing R_0 leads to
 239 decreasing the inter-epidemic period from 5 years to 3 years.

240 *Scenario Two (up to two vaccinations and immunity is permanent = immediate post-vaccine era)*

241 Turning to the successful post-vaccine era (and assuming life-long immunity), Fig. 3 (b) and (d)
 242 show a massive decrease of mumps infections consistent with observed data 1988-2003, where
 243 waning immunity was not yet an important factor and the number of cases overall dramatically
 244 decreased due to the decreased pool of susceptibles, in turn due to vaccination. Again, this helps to
 245 confirm that the model successfully models historical data.

246 *Scenario Three (up to two vaccinations and immunity wanes)*

247 Fig. 3 (c) (resp. Fig.3 (d)) shows model prediction against observations from Scotland in the post-
 248 vaccine era (2004-2016, resp. 1996-2016). Fig. 3 (c) shows pattern of mumps outbreaks from 2004 to
 249 2016 as waning immunity begins to be more relevant. The simulated data (black solid line) displayed
 250 in Fig. 3 (c) depicts patterns of mumps dynamics qualitatively similar to observed data (gray solid
 251 line). Mumps is notoriously under-reported [47] as, especially for those in whom immunity has
 252 waned, the disease is often milder (and infected do not seek medical attention). Our model has no
 253 notion of “level” of infection, therefore sub-clinical, mild, and serious infections are all counted and
 254 contribute to disease transmission. Observed data is scaled by two to compensate for under-reporting
 255 of mumps. This is a conservative estimate, based on higher uptake of vaccine in Scotland than in
 256 Germany [47]. This is discussed further in section 6.

257 Fig. 3 (d) shows that 2005/2015 years were the dominant period reflecting the highest peaks of
 258 mumps infection. Some notable gaps are observed (2009, 2010 and 2012); the observed mumps
 259 dynamics are inherently stochastic and noisy. Fig. 3 (c,d) depicts that the simulated data for the year
 260 2016 follows the same patterns as observed data, where the number of infected start to decrease.
 261 Qualitatively, the simulation results show that even if vaccination is applied, mumps is occurring
 262 each year, where the seasonal patterns of our model depict that the infection increases rapidly over
 263 the last few months of the year and the high peak is reached early at the start of the year. This is
 264 broadly in agreement with observed data.

265 Vaccination coverage dips in this period, but this is not the main factor leading to the resurgence and
 266 sustainability of mumps, nor is seasonality on its own (as above). We investigate the variability of
 267 vaccination coverage by ranging its value from [75 - 95], where 75% is the minimum value related to
 268 the threshold level and 95% is the maximum value of applied vaccine coverage in Scotland. Fig. 5
 269 (see Appendix 3) shows that increasing vaccine coverage leads to a decrease in the peak of infected¹
 270 (from 1694 to 1413). This is 16%, and still produces a large number of cases. Therefore, increasing
 271 the vaccination coverage does not prevent disease occurrence. In addition, we note that all
 272 experiments (vaccination coverage ranging from [80 – 95]) settle into a ten year pattern of gently

¹ Average number of infected corresponds to the average of the highest peaks during 100 years of simulations.

273 damping oscillations (100 years of simulation), where the large oscillations are up to 2045, and
 274 thereafter the outbreaks become more and more regular in height.

275 To further investigate the impact of waning immunity Fig. 6 depicts separately those infected-
 276 unvaccinated and those infected-vaccinated against natively susceptible and modified susceptible
 277 over 100 years of temporal prediction. As expected, due to increasing levels of vaccinated individuals
 278 in the population, the number of natively susceptibles and infected-unvaccinated decreases over time,
 279 reaching a steady state of infection of around 200 individuals. Conversely, waning immunity leads to
 280 an increase in the number of modified susceptible and infected-vaccinated, settling into a ten year
 281 pattern with peaks of between 800 and 1200. Therefore, waning immunity and its effects are the
 282 dominant portion of any epidemic.

283 *Scenario Four (additional booster - up to three vaccinations and immunity wanes)*

284 Further, we consider scenario 4: the impact of increasing the period of immunity by applying an
 285 additional dose of MMR [44]. This could be similarly done by increasing immunity by increasing the
 286 efficacy of the vaccination [43]. We investigate increasing immunity duration in steps from 10 to 80
 287 years (broadly, life expectancy). Fig. 7 compares these scenarios and shows that the average of the
 288 number of infected individuals at the peak of each outbreak decreases with increasing duration of
 289 immunity, as expected.

290 **5 Sensitivity analysis**

291 The results above depend on precise parameter values, therefore we used sensitivity analysis to show
 292 that the qualitative results of periodic large outbreaks hold across the range. We identify significant
 293 parameters reproducing first the observed data, and second leading to the low level endemic state.
 294 Table 2 shows the impact on epidemic amplitude and the periodicity of damping cycles of a series of
 295 experiments during 100 years of simulation varying model parameter values for: transmission rates
 296 ($\beta_1, \beta_2, \beta_3$), infectious period (γ), incubation period (α), immunity duration (τ, δ) and vaccination
 297 rate. The values of the remaining parameters (birth rate, death rate and immigration rate) are fixed.

298 For all analysis we used ANOVA as implemented in Minitab [48]. The full details of the analysis are
 299 in Appendix 2: as expected, only varying transmission rates and immunity duration impact on results.
 300 Increasing R_0 leads to a decrease in period between large outbreaks and therefore an increase in the
 301 number of oscillations (see Fig. 8, Appendix 3). Smaller immunity durations increase the pool of
 302 susceptibles faster and therefore lead to larger and earlier epidemics.

303 **6 Discussion**

304 Our analysis shows that mumps epidemics will continue, with larger outbreaks of ~1200 every 10
 305 years as shown in Fig 6, eventually settling into an endemic state. This is despite high vaccination
 306 coverage against mumps (87- 95%) since 1988 in Scotland [28] (well above the estimated herd
 307 immunity threshold of 75-86% [14]).

308 In this paper, we have presented the results of mathematical modelling using Bio-PEPA, identifying
 309 the impact of vaccination and waning immunity in the mumps component of the MMR vaccine. Even
 310 though vaccination has been ongoing since 1988, thus largely preventing mumps in children, our
 311 results show that waning immunity is the main factor in a repeated pattern of outbreaks. Simulations
 312 and analysis undertaken showed that waning immunity over 10 years leads to the highest number of
 313 infected and to the longest inter-epidemic period for larger outbreaks.

314 The first part of this study was to build a seasonal model which reproduces the patterns of the
315 observed data in three scenarios: no vaccination, initial post-vaccine period with immunity for life,
316 and with waning of vaccine-induced immunity as suggested by several sources [7, 8, 9, 10]. Those
317 show that mumps is present in previously vaccinated individuals with the majority of those affected
318 being university students. While based on Scottish data this is not a peculiarly Scottish phenomenon:
319 for example, in the US [1], Korea [8] and the Netherlands [9] adolescent individuals were notified as
320 infected despite high vaccine coverage. In these countries, it was observed that the majority of cases
321 were in young adult (18 to 25 years) who have been fully vaccinated. In the US, where the first dose
322 of MMR was introduced in 1977 and the second dose in 1990, the outbreak occurring in 2006
323 reached 6584 cases, 63% of whom received two doses of vaccine. For this country it was reported that
324 in 1982 the incidence rate was reduced to 97% and the three year cycles observed in the pre-vaccine
325 era disappeared. Moreover, in 2005, one year before the resurgence of the outbreak occurred in 2006,
326 the incidence rate was damped to up to 99% where the vaccine coverage reached 91.5%. In the
327 Netherlands, the large epidemic which occurred in 2004 led to the reintroduction of mumps as a
328 notifiable disease. This followed its removal from the notifiable disease register in 1999 as a
329 consequence of low outbreaks and vaccination coverage of at least one dose of MMR of at least 93%
330 since the introduction of routine vaccine in 1987. In Korea, the epidemic of 2013-2014 showed that
331 99% of infected individuals aged from 13 to 18 years have been fully vaccinated. It is worth noting
332 that Korea is not that different from other countries as in the pre-vaccine era the epidemic cycles
333 were identified at 4 to 5 years and the mean age of infection at 4 to 6 years which shifted to teenagers
334 in the recent outbreaks (2007 and 2013) in time when vaccination coverage rose to 90%.

335 Waning immunity is expressed in our model by including an additional compartment of modified
336 susceptible, which is increased by vaccinated individuals (MMR1 and MMR2) losing their immunity.
337 We find that assuming 5 years of MMR1 vaccine-induced immunity (resp. 10 years of MMR2
338 vaccine-induced immunity) generates simulation results consistent with more recent mumps post-
339 vaccine data from Scotland (2004-2015). In addition, as our model suggests a ten-year-long gradually
340 damping oscillation, the following trajectory of mumps disease would show a decrease in 2016 and
341 so on, building back up from 2020 to another high peak in the year 2025. The most recent data
342 provided by HPS has confirmed this prediction, where the year 2016 depicts 215 cases compared to
343 2015 which defines 836 cases. Although our estimates of the amplitude of mumps epidemics are
344 higher than observed data, we conjecture that this can be explained by a low level of reporting.
345 Anecdotally, cases of mumps in vaccinated individuals have much milder symptoms and therefore
346 may be undetected [43, 47, 49, 50].

347 By considering different values of immunity duration (scenario 4) we can estimate the time needed to
348 reverse the epidemic trend and eliminate mumps. This models the situation that, for example, a new,
349 more effective, vaccine is introduced, or a third vaccine dose is introduced into the national
350 programme. This is shown in Fig 7. Even extending immunity to 80 years, a reasonable lifespan,
351 mumps outbreaks still occur. Only by further increasing immunity duration to 150 years eliminates
352 mumps outbreaks, assuming no perturbations occur such as a new vaccine or new strain of mumps.

353 It is worth noting that the basic reproductive number R_0 for the pre-vaccine era is estimated at 10.5
354 which falls in the range [7-14] as cited in literature [11, 39] and for the post-vaccine era R_0 is
355 estimated at 6 where in the literature it is quoted at [4-7] [29, 51]. Recall that R_0 indicates the number
356 of secondary infections, clearly showing that the number of doses of vaccination and immunity
357 duration has a great impact on decreasing infectious contacts.

358 Cumulatively, our findings suggest that the more "unprotected" individuals (who were either never
359 vaccinated or lost their immunity), the shorter the period between two high peaks of epidemic
360 outbreak (note the number of cycles in Table 2 for varying values of R_0). In addition, in both cases
361 related to scenarios 1 and 3 (No vaccination and waning immunity), an earlier high peak of mumps is
362 expected. This occurs because the pool of susceptibles is increasing faster as those vaccinated lose
363 their immunity and move to the susceptible state (scenario 3), or the pool of susceptibles is
364 decreasing faster when no vaccination is applied and R_0 is higher (scenario 1). Clearly, controlling
365 the number of susceptible individuals has a great impact on controlling disease. As argued by Gay
366 [52]: to achieve elimination of an epidemic, low levels of susceptible individuals should be
367 maintained, leading the basic reproductive number (R_0) to be less than 1. We do this here by
368 adjusting immunity duration.

369 These conclusions illustrate an enhanced understanding of mumps disease in response to mass
370 immunization gained through mathematical modelling. Further, our multi-disciplinary team could
371 explore the potential impact of further vaccination on cyclic outbreaks. Our conclusion for public
372 health services is that they should urge vaccine uptake in those eligible since a high degree of
373 protection is offered by the vaccine overall for those under 18. Considering the possible economic
374 cost/benefit of a third vaccine dose, it seems that while there would be an increased period of
375 immunity, the cyclic outbreaks would continue at about 2/3 the current level, therefore this would not
376 offer significant advantages over the present situation. The Joint Committee on Vaccination and
377 Immunization² do not consider these large outbreaks of particular concern, since there has been no
378 formal discussion to introduce a 3rd vaccine dose into the national programme.

379 We suggest further study with this model could include vaccination programmes targeted to those
380 subject to waning immunity or at higher risk due to social mixing in a diverse population (as in
381 higher education). Such a model might also include economic factors to allow the effect of targeted
382 programmes to be more precisely evaluated. Another interesting facet would be to bring more
383 attention to the level of immunity by analysing the vaccine/virus content and detect eventual
384 discrepancy between vaccine strain and mumps outbreak. This might also be linked with a data
385 science approach to analysing serology of confirmed cases. There are further opportunities to use
386 data science to analyse other features, such as geographic distribution. These developments would
387 allow an enhanced version of Fig. 6 showing waves of outbreaks related to waning immunity,
388 evolution of strains of mumps, and locality.

389 **7 Conflict of Interest**

390 *The authors declare that the research was conducted in the absence of any commercial or financial*
391 *relationships that could be construed as a potential conflict of interest.*

392 **8 Author Contributions**

- 393 • The Conception or design of the work: C.Shankland, D.Hamami, K.Pollock
- 394 • Data collection: R.Cameron, K.Pollock
- 395 • Data analysis and interpretation: C.Shankland, D.Hamami, K.Pollock

² UK body advising government health policy on vaccination and immunisation.

- 396 • Drafting the article: D.Hamami, C.Shankland
- 397 • Critical revision of the article: C.Shankland, K.Pollock, D.Hamami, R.Cameron
- 398 • Final approval of the version to be published: C.Shankland, K.Pollock, D.Hamami,
399 R.Cameron

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509 **10 Appendix 1: Bio-PEPA Model**

510 A Bio-PEPA model, illustrated below, is defined by three main components: species, functions of
 511 species dynamics and rates at which those species evolve. Modelling mumps in Bio-PEPA requires
 512 describing fully those features accordingly to the model in Fig. 2 and its description above.

513 *Rates.* All rates fully described in Table 1 are reported in Bio-PEPA code, from line 1 to 12. In
 514 addition, Bio-PEPA defines the parameter “location” (from line 13 and line 18). As in our model, the
 515 population is considered homogeneous, therefore all individuals belong to the same space.
 516 Seasonality is expressed by using the Heaviside function (H). As noted by Marco et al. [53]: ”
 517 Heaviside function (H) is used to switch customised behaviours on or off in the kinetic laws, this
 518 gives a binary valued function from time”. The lines from 19 to 22 code two seasons. The system
 519 moves instantaneously from the high epidemic season defined from October to May to the low
 520 epidemic season defined from June to September.

521 *Species and Functional rates (KineticLawOf).* According to the compartments shown in Fig. 2, seven
 522 species are defined: S1, S2, V1, V2, E, I, R. Species carry out actions (**kinetic laws**) leading to
 523 increase/decrease their level (from line 24 to 40). Actions occur at a rate determined by the kinetic
 524 law. Most of these kinetic laws are simple mass action terms defined by the parameters described in
 525 the Table 1. Since species interact, the dynamics of each species may affect the level of other species.
 526 The scale of this dynamic is bounded by the functional rate specified for each species. For example
 527 the action described in line 34, related to incubation and used both by species “E” and “I”, leads to a
 528 decrease in the Exposed species (line 43) expressed by the operator “<<”, while it leads Infected
 529 species to increase using the operator “>>”. Bio-PEPA species can carry out different activities at
 530 each time step, by using the operator ‘+’.

531 The last line of the model (line 48) defines the interaction between species, and their initial sizes.

532 **Parameters**

533 1 D_R = 0.000037;
 534 2 Beta1 =0.80;
 535 3 Beta2 =1.03;
 536 4 Beta = 0.45;
 537 5 Mu2= 0.0000028;
 538 6 Mu3= 0.000025;
 539 7 Mu1 = 0.0000021;
 540 8 Alpha = 0.05;
 541 9 Gama = 0.167;
 542 10 imrate1 =0.07;
 543 11 Tau= 0.00034;
 544 12 Delta=Tau/2;
 545 13 sizeOutside = 110000;
 546 14 sizeLocal = 5300000;
 547 15 location world : size =5200000 , type = compartment;
 548 16 location Local in world: size = sizeLocal, type = compartment;
 549 17 location Local in world: size = sizeLocal, type = compartment;
 550 18 location Outside in world : size = sizeOutside, type = compartment;
 551 19 thigh = 4;
 552 20 tlow = 9;
 553 21 month = floor(time/30);
 554 22 season_time = 1-H(((month - 12*floor(month/12)) - tlow)*(thigh-(month - 12*floor(month/12)))));
 555 23 N = (S1@Local +E@Local + I@Local + R@Local +S2@Local + MMR1@Local + MMR2@Local);

556 **Kinetic Laws**

557 24 kineticLawOf BIRTH1: $\text{Mu1} * \text{N}$;
 558 25 kineticLawOf BIRTH2: $\text{Mu2} * \text{N}$;
 559 26 kineticLawOf BIRTH3: $\text{Mu3} * \text{N}$;
 560 27 kineticLawOf MMR1_S2: $\text{MMR1@Local} * \text{Tau}$;
 561 28 kineticLawOf MMR2_S2: $\text{MMR2@Local} * \text{Delta}$;
 562 29 kineticLawOf Death_MMR1 : $\text{D_R} * \text{MMR1@Local}$;
 563 30 kineticLawOf Death_MMR2 : $\text{D_R} * \text{MMR2@Local}$;
 564 31 kineticLawOf immigration : $\text{imrate1}/10000$;
 565 32 kineticLawOf S1_E: $(\text{Beta1} * \text{S1@Local} * \text{I@Local})/\text{N} * (\text{season_time})$
 566 $+ (1-\text{season_time}) * (\text{Beta} * \text{S1@Local} * \text{I@Local})/\text{N}$;
 567 33 kineticLawOf S2_E: $(\text{Beta2} * \text{S2@Local} * \text{I@Local})/\text{N} * (\text{season_time})$
 568 $+ (1-\text{season_time}) * (\text{Beta} * \text{S2@Local} * \text{I@Local})/\text{N}$;
 569 34 kineticLawOf E_I: $\text{Alpha} * \text{E@Local}$;
 570 35 kineticLawOf I_R: $\text{Gama} * \text{I@Local}$;
 571 36 kineticLawOf Death_S1: $\text{D_R} * \text{S1@Local}$;
 572 37 kineticLawOf Death_I: $\text{D_R} * \text{I@Local}$;
 573 38 kineticLawOf Death_E: $\text{D_R} * \text{E@Local}$;
 574 39 kineticLawOf Death_S2: $\text{D_R} * \text{S2@Local}$;
 575 40 kineticLawOf Death_R: $\text{D_R} * \text{R@Local}$;

576 **Species**

577 41 $\text{S1} = (\text{BIRTH1},1) \gg \text{S1@Local} + (\text{S1_E},1) \ll \text{S1@Local} + \text{Death_S1} \ll \text{S1@Local}$;
 578 42 $\text{S2} = (\text{S2_E},1) \ll \text{S2@Local} + \text{Death_S2} \ll \text{S2@Local} + (\text{MMR2_S2},1) \gg \text{S2@Local} + (\text{MMR1_S2},1) \gg$
 579 S2@Local ;
 580 43 $\text{E} = (\text{S1_E},1) \gg \text{E@Local} + (\text{S2_E},1) \gg \text{E@Local} + (\text{E_I},1) \ll \text{E@Local} + \text{Death_E} \ll \text{E@Local}$;
 581 44 $\text{I} = (\text{E_I},1) \gg \text{I@Local} + (\text{I_R},1) \ll \text{I@Local} + \text{Death_I} \ll \text{I@Local} + \text{immigration}[\text{Outside} \rightarrow \text{Local}](.)\text{I}$
 582 $+ (\text{S1_E},1) (.) \text{I} + (\text{S2_E},1) (.) \text{I}$;
 583 45 $\text{R} = (\text{I_R},1) \gg \text{R@Local} + \text{Death_R} \ll \text{R@Local}$;
 584 46 $\text{MMR1} = (\text{BIRTH2},1) \gg \text{MMR1@Local} + (\text{MMR1_S2},1) \ll \text{MMR1@Local} + \text{Death_MMR1} \ll$;
 585 47 $\text{MMR2} = (\text{BIRTH3},1) \gg \text{MMR2@Local} + (\text{MMR2_S2},1) \ll \text{MMR2@Local} + \text{Death_MMR2} \ll$;

586 **Model component**

587 48 $\text{S1@Local}[110000] \ll \text{S2@Local}[305500] \ll \text{E@Local}[0] \ll \text{I@Local}[20] \ll \text{R@Local}[3018600] \ll$
 588 $\text{MMR1@Local}[29250] \ll \text{MMR2@Local}[276250] \ll \text{I@Outside}[100000]$

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603 11 Appendix 2: Sensitivity analysis

604 1: Incubation period experiments

605 The analysis per ANOVA is carried out for 14 experiments where the incubation period varied from
606 12 to 25 days per one step day. The results indicate that at 95% of confidence, no significant
607 statistical differences between experiments ($p = 0.968$) and then the null hypothesis (the means of
608 experiments are equal) cannot be rejected. Hsu's MCB test and Tukey test imply that varying
609 incubation period does not affect the number of infected; however, using simulations we can look at
610 cycles. 100 years of simulations show that by increasing the incubation period the periodicity
611 changes from 8 to 11 cycles.

612 Analysis 2: Infectious period experiments

613 Varying the infectious period from 6 to 9 days per one step day, indicates no significant statistical
614 differences ($p = 0.114$). However, the results validated by the Tukey test are in contrast with the
615 Hsu's MCB test results. While the former shows no significant differences, the latter shows
616 significant differences between an infectious period of 6 days (1st experiment) and the one of 9 days
617 (4th experiment). In fact, the analysis shows clearly that the mean of the 4th experiment (2739) is
618 higher than the others (1808, 2113, 2276). In addition the simulation results show that increasing the
619 infectious period increases the amplitude of the epidemic where the main gap is depicted at the first
620 peak.

621 Analysis 3: Transmission rates experiments

622 Transmission rate experiments are based on changing the basic reproductive number R_0 from 4 to 11.
623 This equates to varying the high transmission rate from 0.44 to 1.83 and the low transmission rate
624 from 0.19 to 0.81. ANOVA analysis shows that experiments are not statistically significantly
625 different ($p = 0.36$). However, simulations over 100 years indicate that increasing the basic
626 reproductive number leads to a decrease in periodicity. As R_0 varies from 4 to 11 the period of cycles
627 per 100 years of simulation varies from 14 to 6 and the number of cycles varies from 7 to 16 cycles.
628 During simulations, it was observed that the first epidemic tends to occur sooner with increasing
629 amplitude as R_0 increases.

630 Analysis 4: Immunity duration experiments

631 The analysis per ANOVA of the different values of immunity duration varying from 10 to 80 years,
632 reveals statistically significant differences. In particular, the analysis depicts four different groups.
633 The first group includes only one experiment (immunity duration = 10 years). The second group
634 includes two experiments (immunity duration = 20 and 30). The third group includes three
635 experiments (30, 40 and 50). The fourth group includes five experiments (40, 50, 60, 70 and 80),
636 where the 2nd group overlaps the third group with one experiment (30) and the third group overlaps
637 the fourth group with two experiments (40, 50). In ANOVA, the experiment which does not share
638 any group is considered significantly different. This implies that experiment one (10) is significantly
639 different from all others. This is because small immunity duration tends to increase the pool of
640 susceptibles faster and the epidemics occur sooner with higher amplitude. Moreover, this analysis
641 supports the idea that immunity duration has a major effect on the epidemic dynamics, while varying
642 incubation period, infectious period and transmission rates do not show such large impact on
643 epidemic curves.

644 Analysis 4: Vaccination coverage experiments

645 Varying vaccination coverage from 75% to 95% in steps of 5 percentage points, indicates at 95% of
646 confidence no significant statistical differences ($p= 0.648$) between experiment and H0. The results
647 validated by Tukey test are similar to those with Hsu's MCB test results which imply that varying
648 vaccination coverage does not affect the number of infected; this fact is confirmed by simulations
649 performed where we can look at cycles. 100 years of simulations show that by increasing the
650 vaccination coverage the periodicity does not change significantly. From 80% to 95% the simulations
651 detect 10 cycles where at 75%, the periodicity of cycles is at 9 years. These findings support the
652 conclusions of DeStefano et al [15] and Donaghy et al [14].

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674 **12 Appendix 3: Mumps data in England and Wales**675 **Table 1.** Model parameters

| Parameter | Description | Value (day) | Formula |
|------------|--|---------------------|---|
| B | Birth rate | $3 \cdot 10^{-5}$ | Number of birth / Total population |
| μ | Death rate | $3.7 \cdot 10^{-5}$ | Number of death / Total population |
| μ_1 | No-vaccination rate | $2.1 \cdot 10^{-6}$ | Birth rate $-(\mu_2 + \mu_3)$ |
| μ_2 | Vaccination rate (MMR1) | $2.8 \cdot 10^{-6}$ | Birth rate * VC1 |
| μ_3 | Vaccination rate (MMR2) | $2.5 \cdot 10^{-5}$ | Birth rate * VC2 |
| τ | Waning immunity rate (MMR1) | $3.4 \cdot 10^{-4}$ | 1/immunity duration of MMR1 |
| δ | Waning immunity rate (MMR2) | $\tau/2$ | 1/immunity duration of MMR2 |
| | Transmission rate for : | | |
| β_1 | - high season and native susceptible | 0.7 | |
| β_2 | - high season and modified susceptible | 0.9 | $\beta = R_0 * \gamma$ |
| β_3 | - low season | 0.4 | |
| T^3 | Inter-epidemic period | [2-5] | $T = 2\pi * \sqrt{A(\frac{1}{\alpha} + \frac{1}{\gamma})}$ [42] where A: mean age of infection |
| $1/\alpha$ | Incubation period | [12-25] | 1/infection rate |
| $1/\gamma$ | Infectious period | [7-9] | 1/recovery rate |
| λ | Immigration rate | 0.07 | Immigration * $\sqrt{\text{population}}$ |

676

677

³ Inter-epidemic period related to a pre-vaccine era

678 **Table 2.** Sensitivity analysis summary**Incubation period**

| | | | | | | | | | | | | | | |
|------------------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|
| Values | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 |
| Amplitude | 2357 | 2316 | 2229 | 2123 | 2020 | 2309 | 2280 | 2153 | 2149 | 2132 | 2020 | 1968 | 1909 | 1927 |
| Period of Cycles | 8 | 9 | 9 | 9 | 9 | 9 | 10 | 10 | 10 | 10 | 11 | 10 | 11 | 11 |

Infectious period

| | | | | |
|------------------|------|------|------|------|
| Values | 6 | 7 | 8 | 9 |
| Amplitude | 1808 | 2132 | 2276 | 2739 |
| Period of Cycles | 10 | 10 | 11 | 10 |

Basic reproductive number

| | | | | | | | | |
|------------------|------|------|------|------|------|------|------|------|
| Values | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
| Amplitude | 1690 | 1708 | 2132 | 2134 | 2256 | 2320 | 2289 | 2407 |
| Period of Cycles | 14 | 12 | 10 | 9 | 9 | 8 | 7 | 6 |

Immunity duration

| | | | | | | | | |
|------------------|------|------|-----|-----|-----|-----|-----|-----|
| Values | 10 | 20 | 30 | 40 | 50 | 60 | 70 | 80 |
| Amplitude | 1873 | 1245 | 909 | 668 | 555 | 440 | 371 | 306 |
| Period of Cycles | 10 | 8 | 7 | 7 | 6 | 5 | 5 | 4.5 |

Vaccination coverage

| | | | | | |
|-----------------------------|------|------|------|------|------|
| Values | 75 | 80 | 85 | 90 | 95 |
| Amplitude (100 years peaks) | 1694 | 1660 | 1552 | 1536 | 1413 |
| Amplitude (10 first peaks) | 1602 | 1587 | 1547 | 1504 | 1410 |
| Period of Cycles | 9 | 10 | 10 | 10 | 10 |

- 679 **Fig. 1** Confirmed mumps cases, Scotland 1988-2016 and MMR vaccine coverage
680 **Fig. 2** Mumps structure
681 **Fig. 3** Predicted incidence of mumps from 2004 to 2016: : (a) Scenario 1- No vaccination, (b) Scenario 2-
682 Vaccination without waning immunity, (c) Scenario 3- Vaccination with waning immunity, (d)) Predicted-
683 Observed data for mumps from 1996 to 2016..
684 **Fig. 4** Inter-epidemic period against basic reproductive rate R_0 for pre-vaccine era
685 **Fig. 5** Infected against vaccination coverage
686 **Fig. 6** The effect of waning immunity: Left axis: Infected-unvaccinated, Infected-unvaccinated/vaccinated.
687 Right axis: natively susceptible and modified susceptible.
688 **Fig. 7** Infected against duration of immunity
689 **Fig. 8** Inter-epidemic period against basic reproductive rate R_0 for post-vaccine era
690 **Fig. 9** Confirmed mumps cases, England and Wales and MMR vaccine coverage
691

Provisional

Figure 01.JPEG

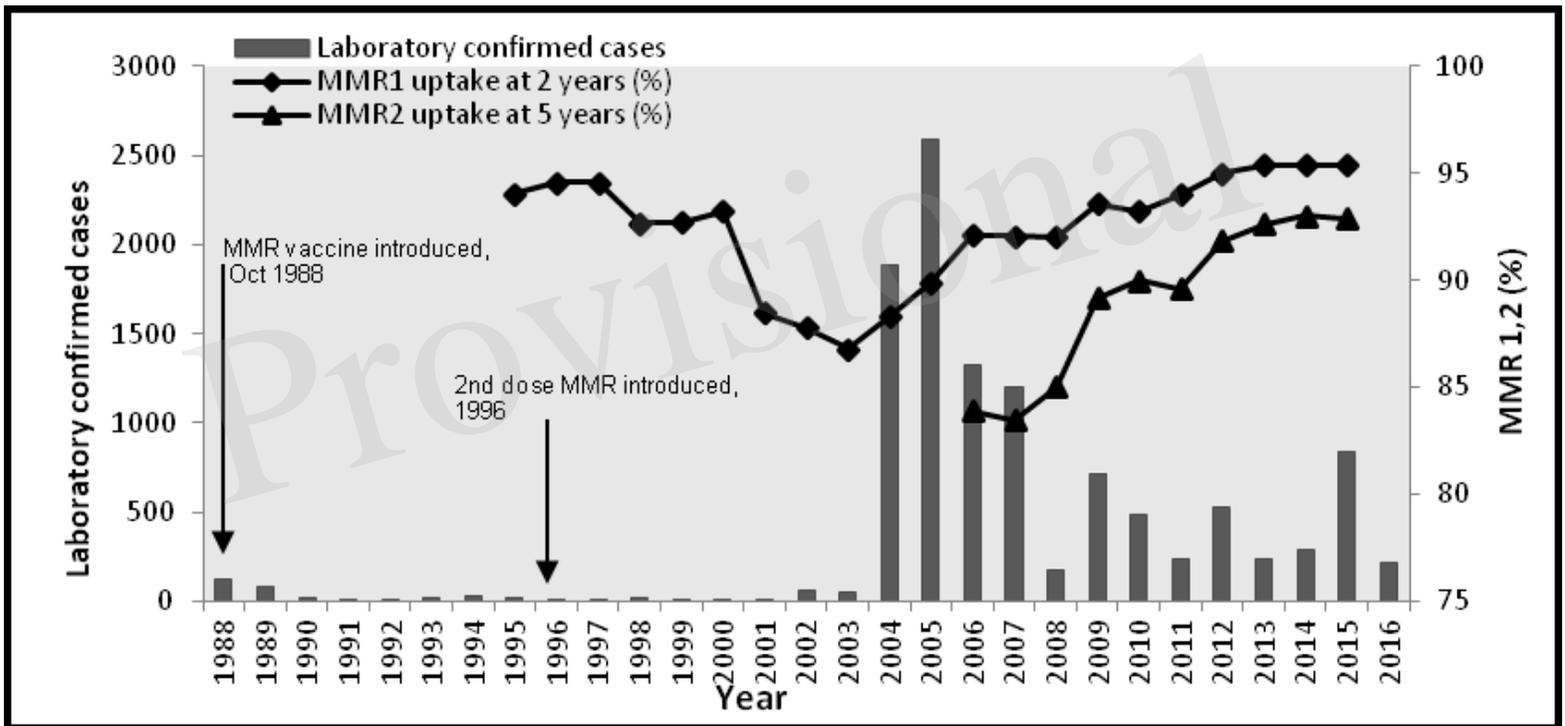


Figure 02.JPEG

Provisional

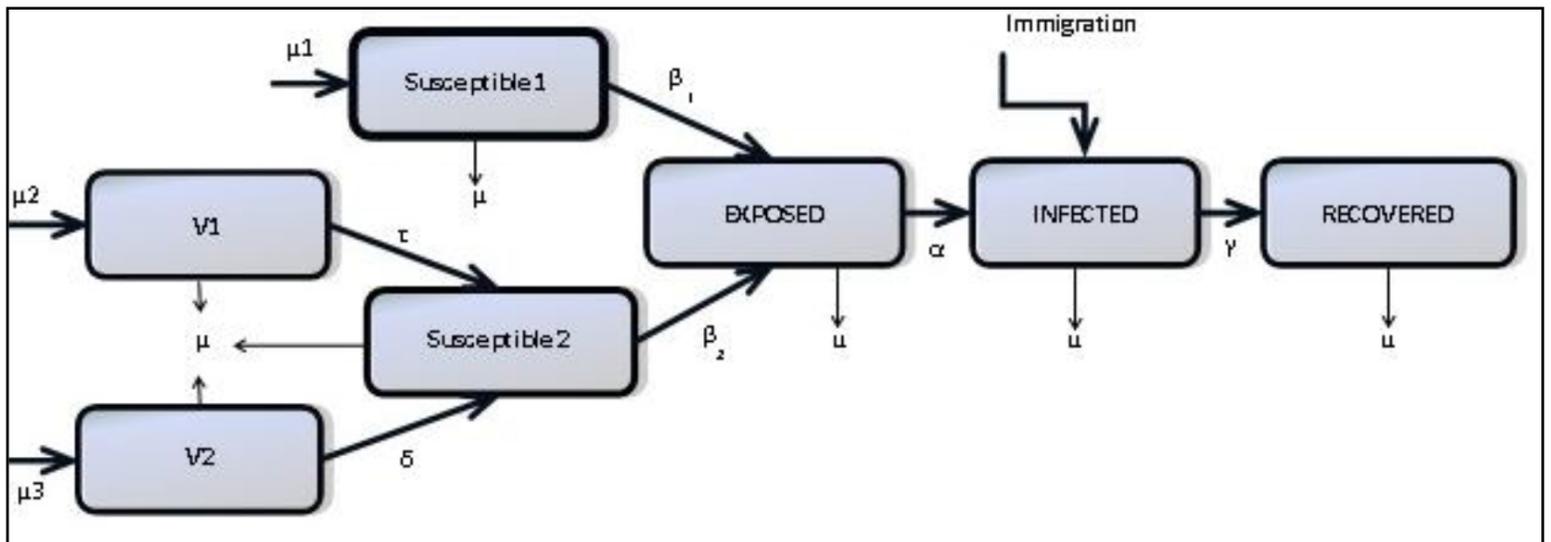


Figure.03.IPEG

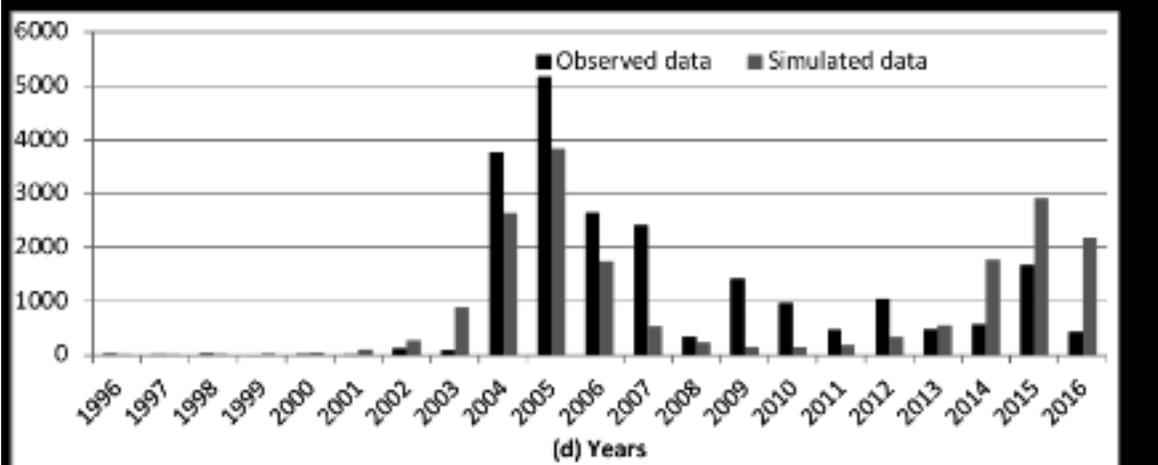
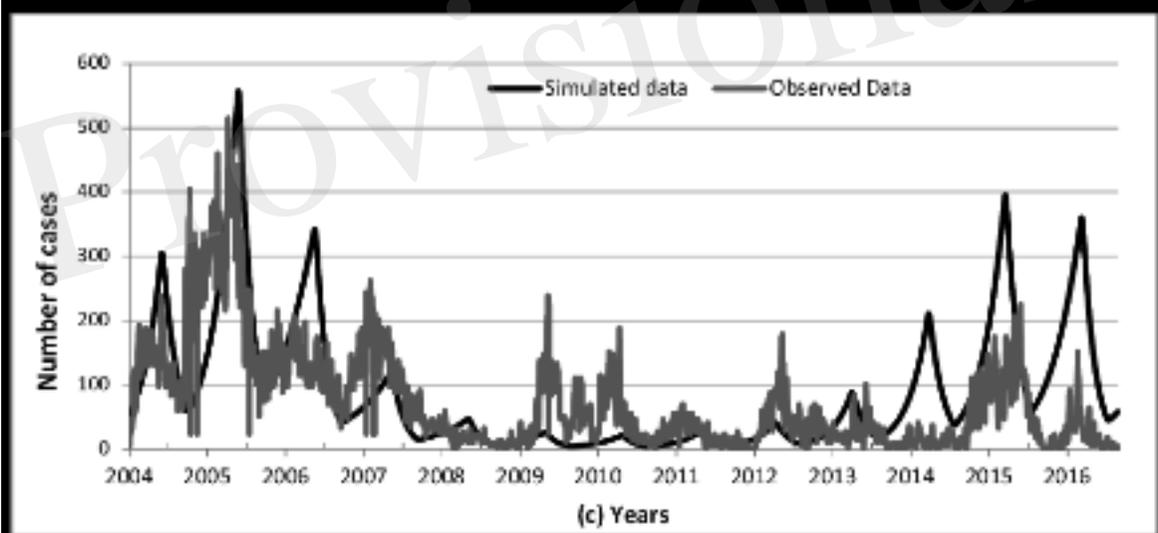
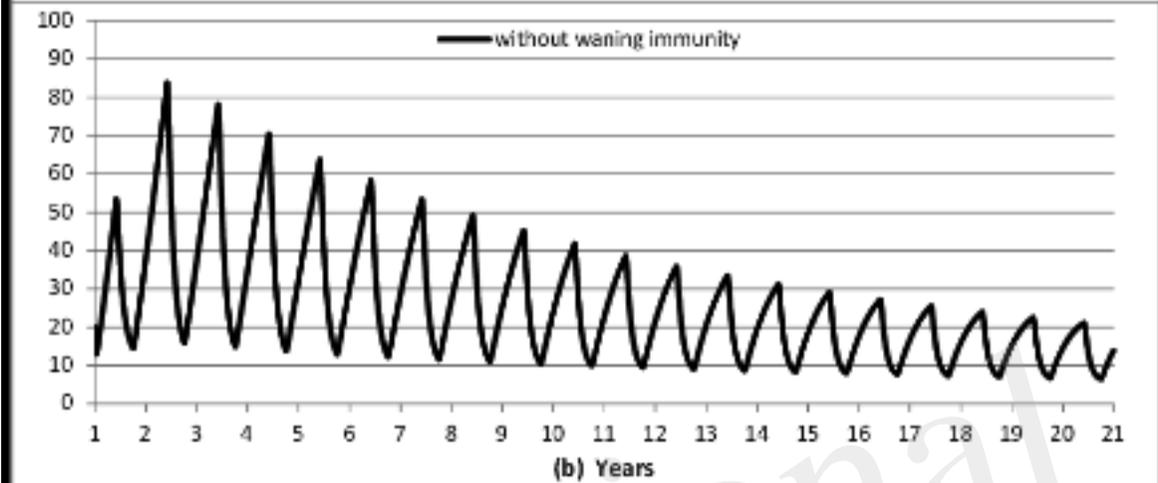
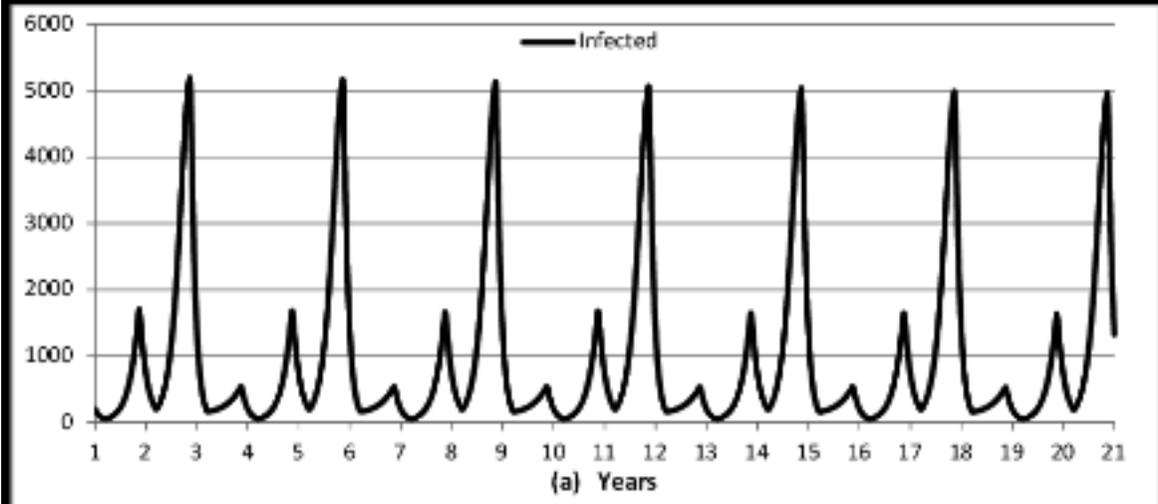


Figure 04.JPEG

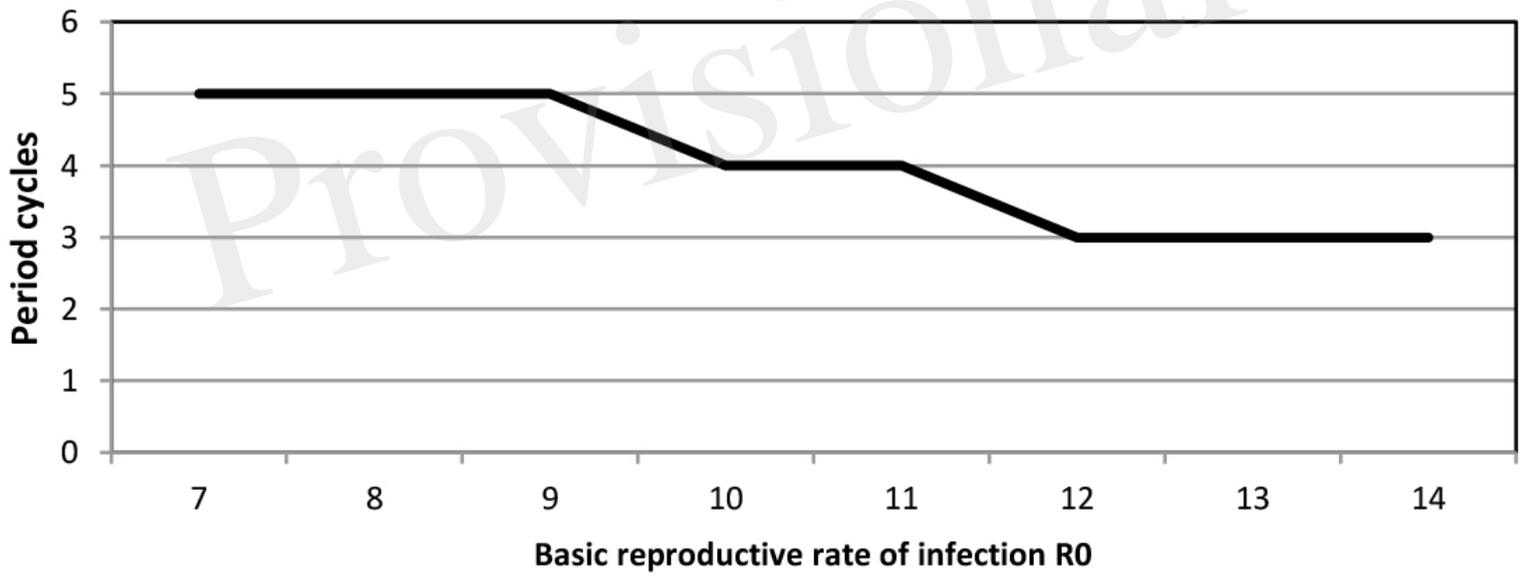


Figure 05.JPEG

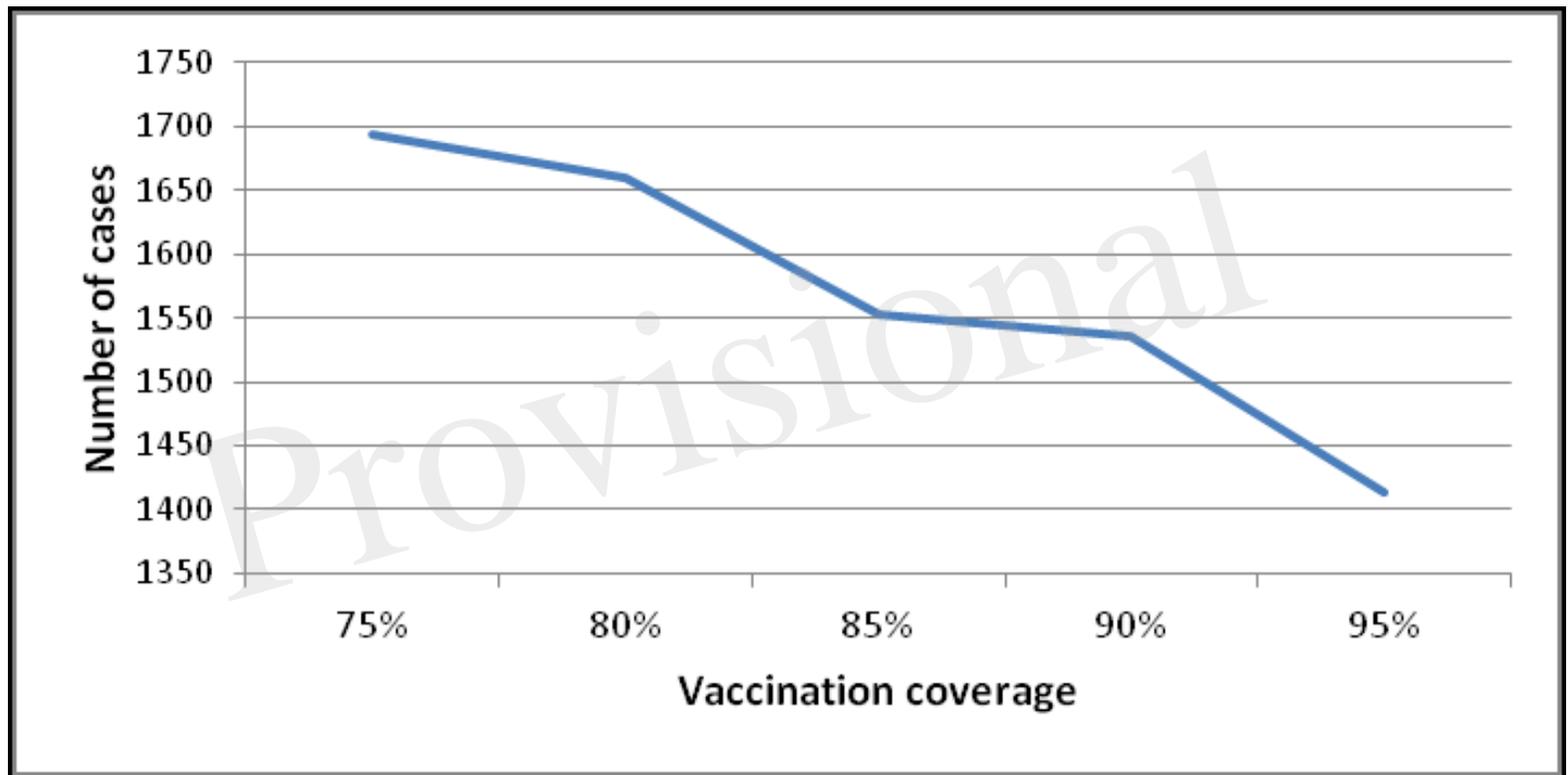


Figure 06.JPEG

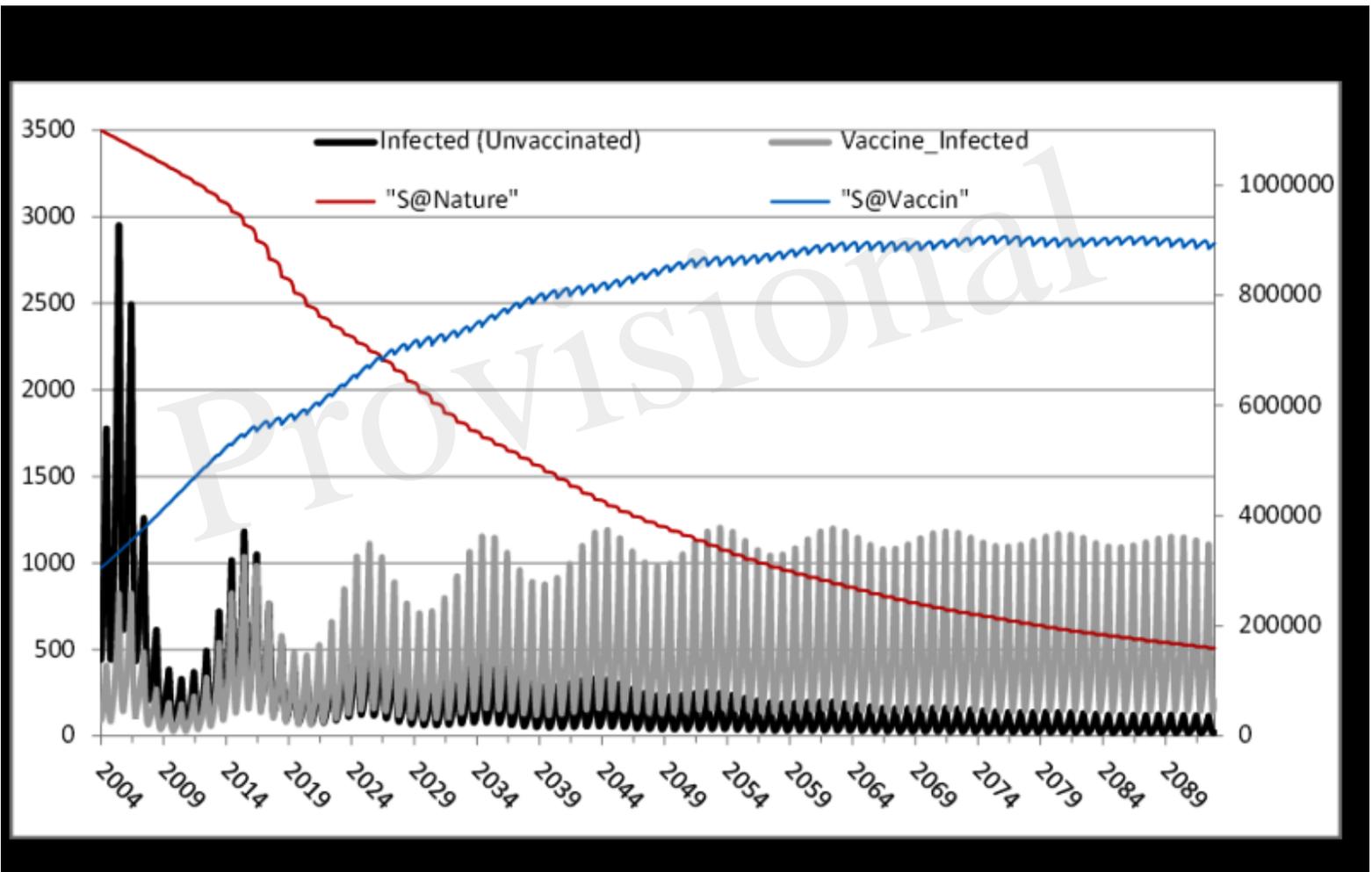


Figure 07.JPEG

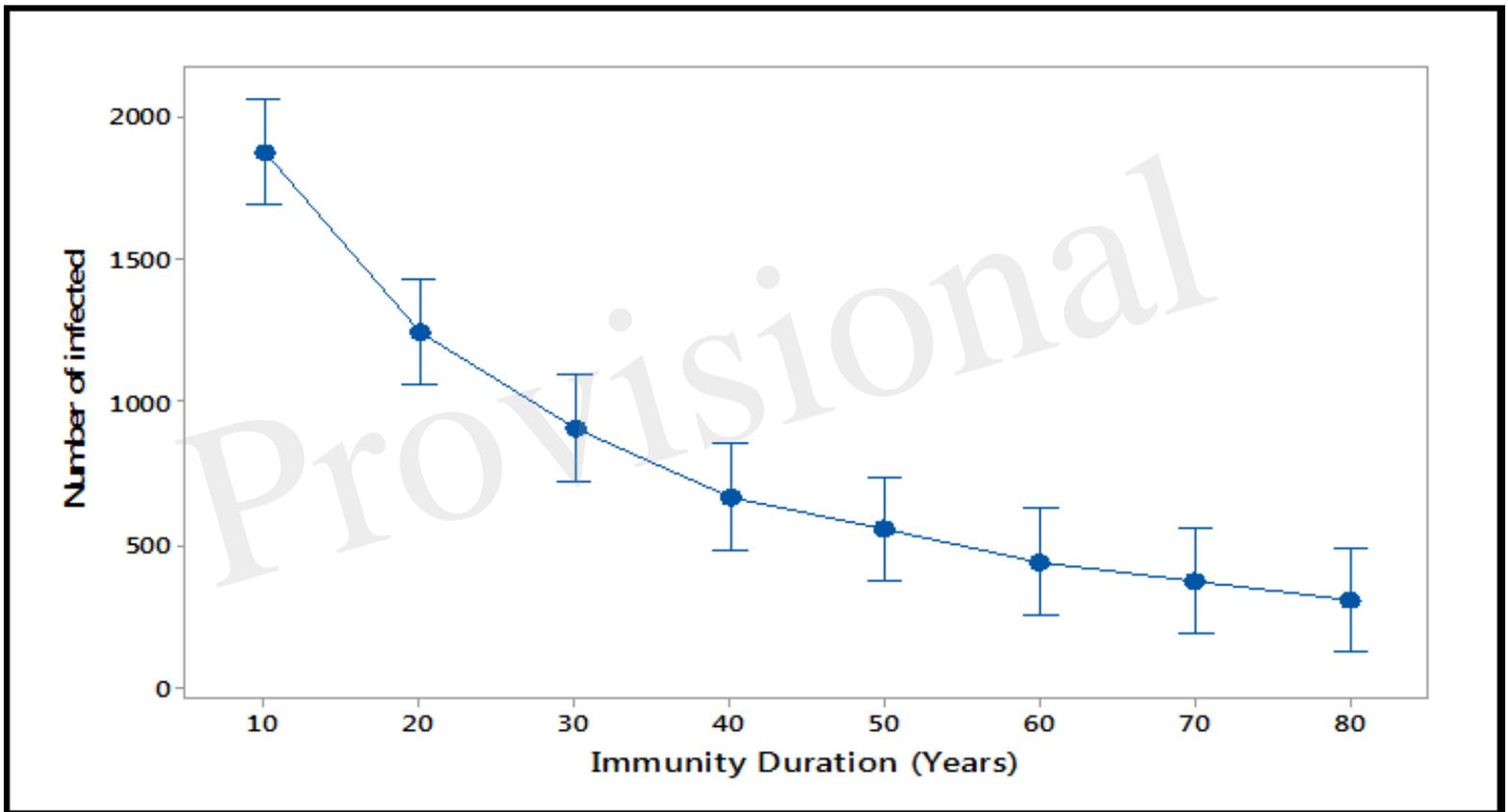


Figure 08.JPEG

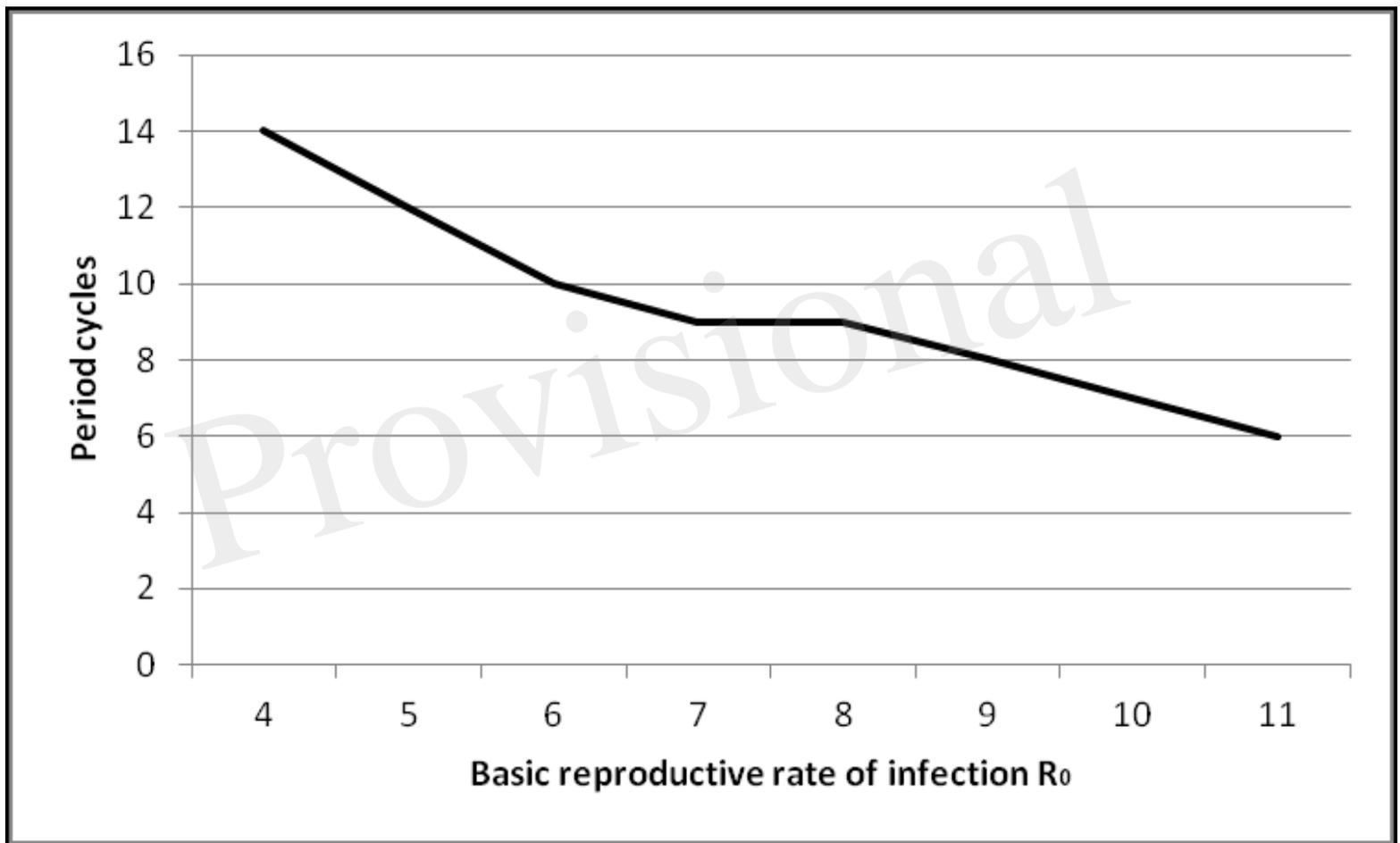


Figure 09.JPEG

