Original article

Imported Infections Versus Herd Immunity Gaps; A Didactic Demonstration of Compartment Models Through the Example of a Minor Measles Outbreak in Hungary

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Abstract

Introduction: In Hungary, where MMR vaccine coverage is 99%, in 2017, a minor measles epidemic started from imported cases due to two major factors – latent susceptible cohorts among the domestic population and the vicinity of measles-endemic countries. Suspended immunization activities due to the COVID-19 surge are an ominous precursor to a measles resurgence. This epidemiological demonstration is aimed at promoting a better public understanding of epidemiological data.

Materials and Methods: Our previous MMR sero-epidemiological measurements (N of total measles cases = 3919, N of mumps cases = 2132, and N of rubella cases = 2132) were analyzed using open-source epidemiological data (ANTSZ) of a small-scale measles epidemic outbreak (2017, Hungary). A simplified SEIR model was applied in the analysis.

Results: In case of measles, due to a cluster-specific inadequacy of IgG levels, the cumulative seropositivity ratios (measles = 89.97%) failed to reach the herd immunity threshold (HIT Measles = 92–95%). Despite the fact that 90% of overall vaccination coverage is just slightly below the HIT, unprotected individuals may pose an elevated epidemiological risk. According to the SEIR model, ≥74% of susceptible individuals are expected to get infected. Estimations based on the input data of a local epidemic may suggest an even lower effective coverage rate (80%) in certain clusters of the population.

Conclusion: Serological survey-based, historical and model-computed results are in agreement. A practical demonstration of epidemiological events of the past and present may promote a higher awareness of infectious diseases. Because of the high R0 value of measles, continuous large-scale monitoring of humoral immunity levels is important.

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Introduction

Testing of acquired immunity and effectiveness of vaccination against infectious diseases has been increasingly important in the design of preventive public health strategies. Resurgence in measles cases in the United States and across Europe has occurred, including in individuals vaccinated with two doses of the vaccine (1). According to the Centers for Disease Control and Prevention (CDC), World Health Organization (WHO) and United Nations International Children's Emergency Fund (UNICEF), measles has already been a global issue and now it has been aggravated by disrupted immunization protocols due to the COVID-19 pandemic (2–5). All six WHO regions have reported disrupted immunization activities, with major adverse effects on routine immunization and mass vaccination campaigns (4). According to CDC reports, in 2020, more than 117 million children were at the risk of missing out on measles vaccines as a consequence of the COVID-19 surge (2). Measles immunity gaps resulting from suspended immunization activities are an ominous precursor to a measles resurgence (4). In Ukraine, one of Hungary's neighboring countries that was already endemic for measles, vaccination has been interrupted in many regions (3). Regarding Europe, ECDC surveillance data have indicated an exceptionally high number of measles cases in 2018, 2019 and 2020 in EU/EEA countries.

Vaccination remains one of the safest and most effective interventions available in public health for the primary prevention of infectious diseases, resulting in both direct and indirect immunity in individuals vaccinated (herd immunity) (6–8). Even though a safe and effective two-dose measles/MMR vaccination schedule has been available in Europe since the 1960s, maintaining high vaccine coverage is still difficult, despite the fact that in Hungary, the MMR vaccine is mandatory and consequently the vaccine coverage is estimated to be at 98-99%. According to our previous publications (9,10) and in agreement with the results obtained by our colleagues (11), there are latent immunization gaps in certain age (or immunization) clusters of

the Hungarian population, with predominance of the ~35-45-year-old adults. These are individuals who form a significant portion of the active labor force of the country, for instance health care workers (HCWs).

Between January 2017 and May 2019, there were 76 reported measles cases in Hungary (12), 54 of which were reported between 21 February and 22 March 2017 (13). Because of the recent outbreaks worldwide, not only of measles, but also mumps and rubella (MMR) infections, and because of waning of immunity over time after vaccination (14–17), the importance of continuous MMR seroepidemiological screening is evident.

Suboptimal vaccine effectiveness in certain clusters of the population has a negative impact on overall vaccination coverage. Small-scale outbreaks suggest that certain measles vaccines – applied during the early phases of the Hungarian vaccination history – failed to elicit the desired immunological response. The resulting immunization gap(s) raise the concern of potential further outbreaks (9,11). The 2020 COVID-19 outbreak called attention to the importance of mathematical modelling of epidemics (18). Based on a reliable model, the timescale and economic impact of the disease can be predicted and preventive countermeasures can be taken (19). Through the example of the measles epidemic in Makó (2017, southeast Hungary), we demonstrated that, in possession of key epidemiological data (e.g. R0 value, estimated vaccination coverage of a given population, number of infected and recovered individuals and duration of the epidemic), a simple open-source mathematical model can give a good approximation of the course of an infection and may provide better general compliance with protective measures.

Materials and Methods

Experimental work

In this seroepidemiological survey, we combined the data from our previous findings with recent measurements, including anti-

measles, -mumps and -rubella antibody level (IgG) determination. Measurements were performed on the automated Siemens BEP 2000 Advance® platform (Siemens AG, Germany), using our self-developed ELISA assays validated by well-established commercial kits, as previously described (9,10). Indirect immunofluorescent microscopy was used a reference (Euroimmun, Germany).

In case of large-scale seroepidemiological measurements, a serum bank consisting of anonymous patient sera was used (N of total measles cases = 3919, N of mumps cases = 2132, and N of rubella cases = 2132) (Ethical License number 2015/5726). Nationally representative samples included randomly selected clinical residual samples, with the exclusion criteria of neonates, children under the vaccination age and severely immunocompromised patients. Samples were collected from the Department of Laboratory Medicine (University of Pécs, Clinical Centre). Serum samples were from all listed age groups participating in this study and they were categorized based on past changes introduced in measles and MMR immunization schedules. Age group determination was based on the landmarks in the history of measles and MMR vaccination schedules in Hungary (Figure 1). Human sera were stored in the accredited laboratory of the Department of Immunology and Biotechnology (University of Pécs, Medical School, Pécs, Hungary) according to quality assurance criteria (ISO 17025).

Population-level result evaluation and seropositivity ratio assessment was performed in relation to the concept of herd immunity threshold (HIT) values (HIT Measles = 92–95%, HIT Mumps = 85–90%, HIT Rubella = 83–86). The study relies on the full virus antigen repertoire-based indirect ELISA method. Therefore, it must be considered a good surrogate, rather than an absolute correlate marker for immunity – as far as Plotkin's nomenclature is considered normative (20–22). We examined vaccination group-related infection- and vaccine-induced antibody titres using the following software: SPSS, Origin Pro, Excel.

SEIR model example and input data

A small-scale measles outbreak in Hungary in 2017 raised questions about the vaccination coverage rate in the country. Experimental results supported the theory of ineffective vaccines, as previously mentioned (9). In spite of its limitations, it seemed reasonable to set up a SEIR model calculation in order to see whether a few percent decrease in effective vaccination could result in a local epidemic. To demonstrate the disease spread in a well-immunized population where latent immunity gaps may be present, input data were based on the data of the 2017 measles outbreak in Makó, southeast Hungary. The following parameters were used to perform the calculations:

Population (N): The epidemic was linked to the small-town hospital. During that year, 65 physicians were responsible for medical attendance of the estimated 30,000 inhabitants of Makó and the surrounding villages. In our model, a population of N = 400-1,000 people was assumed, including patients, health-care workers and family members.

Number of infected individuals (I): A total of 29 cases were reported.

Incubation time and contagious period: The incubation time for measles ranges from 10 to 12 days on average, an infected person can be contagious even 1-2 days before the first characteristic symptoms are visible, up to 4 days after the rashes appear. In our model, the incubation time (Tinc) was assumed to be 10 days, whereas the contagious period (Tcont) was 6 days. Based on these values, and parameters were determined by equations (5) and (6).

Reproduction rate ranging from 12 to 18 can be found in the literature and both values were tested. The higher value is applicable to communities where no social distancing is present and the ratio of vaccinated or immunized inhabitants is low. In Central Europe, the use of the lower value seems more rational, although this specific epidemic was kept mainly in a hospital, where circumstances promote the spread of the infection. In this case, the start of

the outbreak was defined as the possible first day of the first patient's infection, while the model was set to stop after the recovery of the last infected person. When it comes to large-scale epidemics, a different approach is used. If no new cases are found after a certain period, the outbreak is over. This time period is usually determined by the incubation time, with a calculation method suggested by the WHO.

Based on the ELISA antibody measurements, it can be assumed that only ~90% of the Hungarian population has effective immunization, which is under the theoretical 92-94% of HIT. In the model, 90% of seroprevalence was assumed, but lower values were also tested subsequently. No additional vaccinated (V) compartment was created and immunized individuals were treated as recovered. Vital dynamics was disregarded due to the short period of the epidemic. Death rate was not taken into consideration either, as no fatalities were observed during the Hungarian outbreak. Calculations were

performed using Microsoft Excel Visual Basic Application (VBA), but the graphs were plotted in Origin. VBA is a built-in feature of the Microsoft Office Suite with several limitations, but its prevalence and the user-friendly computer language makes it suitable for educational purposes.

Results

Changes and historical data regarding epidemics in the Hungarian measles/MMR vaccination schedule (23–25) have been plotted on a timeline in order to evaluate seroepidemiological data accordingly. Figure 1 shows changes in measles and MMR vaccination schedules in Hungary since the introduction of the vaccine (1969). High age-specific attack rates characterizing major epidemics (1980-81 and 1988-89) along with 93%-99% of vaccine coverage evidence insufficiencies of the early vaccination program.
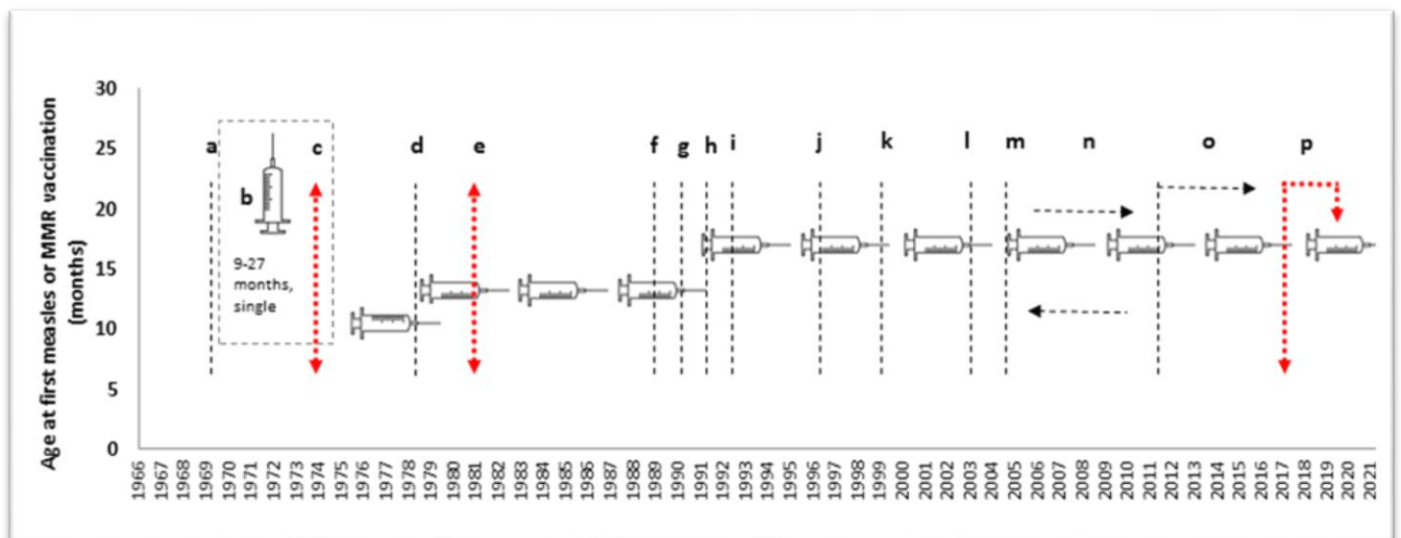

Figure 1. Measles and MMR vaccination schedules in Hungary
(a) Vaccination against measles was introduced in Hungary in 1969. (b) From 1969 to 1974, a single dose of measles vaccine was administered in mass campaigns to persons aged 9-27 months. (c) After vaccination was implemented, the incidence rate decreased until 1973-74, when large epidemics occurred primarily in unvaccinated 6-9-year-olds. (d) The recommended age for vaccination was 10 months until 1978, when it was changed to 14 months. (e) After the 1980-81 epidemic, persons born between 1973 and 1977, who received vaccine when the recommended age was 10 months, were revaccinated. (f) The 1988-89 epidemic mainly affected persons aged 17-21, who had been targeted to receive vaccine during mass campaigns in the first years of the vaccination program in Hungary. After 1989, children were re-vaccinated at the age of 11 with a monovalent measles vaccine in a scheduled manner. Also, in 1989, the rubella vaccine was introduced. (g) In 1990, measles-rubella bivalent vaccines were introduced. (h) The administration of the first vaccine at the age of 14 months lasted from 1978 to 1991. Also, in 1991, the measles-mumps-rubella trivalent vaccine was introduced. (i) In 1992, the administration of the first MMR vaccine was shifted to 15 months of age. (j) In 1996, the MERCK MMR II vaccine (Enders' Edmonston

strain, live attenuated) was introduced. (k) In 1999, measles-mumps-rubella revaccination replaced the monovalent measles vaccine. Also, in 1999, the GSK PLUSERIX vaccine (Measles Schwarz Strain) was introduced. (l) In 2003, the GSK PRIORIX vaccine was introduced. (m) Between 2004 and 2005, the MERCK MMR II vaccine was used. (n) Between 2006 and 2010, the GSK PRIORIX vaccine was in use. (o) Starting from 2011, we have been using a Sanofi-MSD product, MMRvaxPro (Measles virus Enders' Edmonston strain, live, attenuated), for vaccination and revaccination of children. GSK PRIORIX is still on the market, commonly used for vaccination in adulthood. (p) Between January 2017 and December 2019, there were 76 reported measles cases in Hungary (according to ECDC Surveillance reports). (Source of information: MMWR Weekly October 06, 1989 / 38(39); 665-668, International Notes Measles – Hungary, http://www.vacsatc.hu, https://www.ecdc.europa.eu)

Figure 2 shows the age or vaccination group-specific seropositivity and seronegativity ratios for measles, mumps and rubella. The lowest seropositivity ratios in terms of anti-measles antibody titres (IgG) were observed in the groups 'Vaccinated between 1969-1977' (87.56%) and 'Vaccinated between 1978-1987' (78.48%). These results are further confirmed by the abovementioned vaccine insufficiencies of the relative periods, described in Figure 1. Regarding the mumps and rubella seroepidemiological survey, in terms of humoral antibody levels, all vaccination groups satisfied the requirements necessary for the achievement of herd immunity.
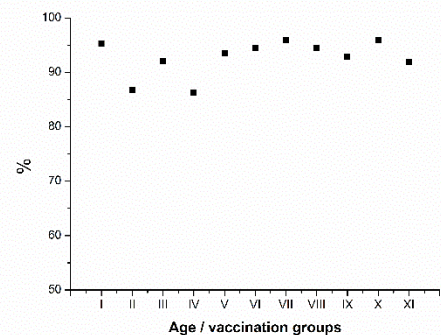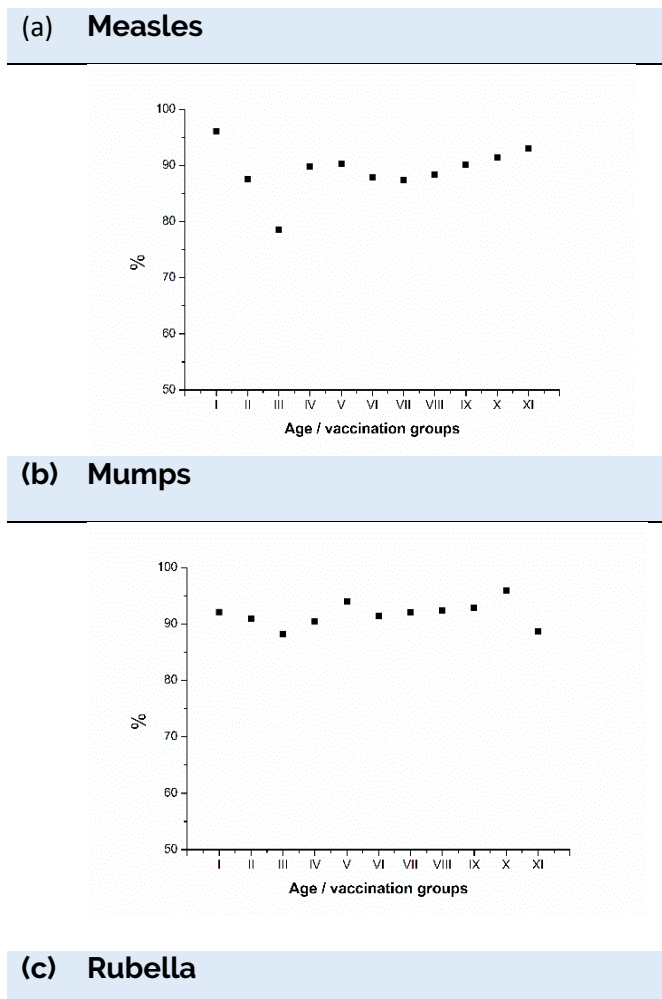
(a) **Measles**

(b) **Mumps**

(c) **Rubella**

Figure 2. Measles, mumps and rubella seropositivity ratios according to vaccination groups

Age / vaccination groups: (I) Individuals born before 1969. (II) Individuals vaccinated between 1969 and 1977. (III) Individuals vaccinated between 1978 and 1987. (IV) Individuals vaccinated between 1988 and 1990. (V) Individuals vaccinated between 1991 and 1995. (VI) Individuals vaccinated between 1996 and 1998. (VII) Individuals vaccinated between 1999 and 2002. (VIII) Individuals vaccinated in 2003. (IX) Individuals vaccinated between 2004 and 2005. (X) Individuals vaccinated between 2006 and 2010 (XI) Individuals vaccinated after 2011. The lowest seropositivity ratio (78.48%) was observed in the anti-measles antibody titres (IgG) in the group 'Vaccinated between 1978 and 1987'.

In case of measles, mumps and rubella cumulative results, the seropositivity ratios were 89.97%, 91.60% and 92.58%, respectively, as shown in Figure 3. Due to previously detailed

cluster-specific inadequacy of humoral antibody levels, the cumulative anti-measles seropositivity ratios also failed to reach the herd immunity threshold (HIT Measles = 92–95%).
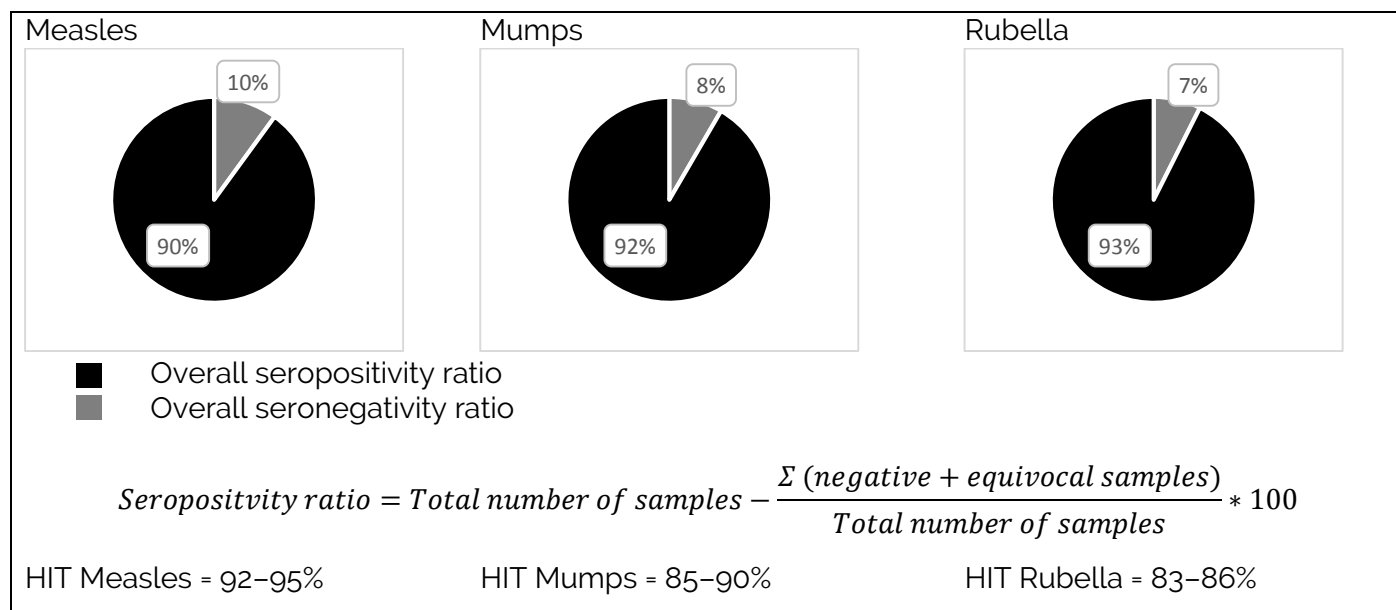

Figure 3. Overall seropositivity and seronegativity ratios

N measles = 3,919; N mumps, rubella = 2,132. In case of measles, mumps and rubella cumulative results, the seropositivity ratios were 89.97%, 91.60% and 92.58%, respectively. The overall ratio of seropositive samples was the lowest in the 'measles' group, where it remained under the threshold value. Seropositivity ratios were calculated as follows:

Using the seronegativity ratio of 89.97% (≈ 90%) obtained by the cumulative data representation of anti-measles (IgG) antibody levels, the model of possible outcomes of a measles outbreak in a hospital as a function of the vaccination coverage rate was investigated. The results of the VBA-based SEIR model of the 2017 epidemic in Hungary are summarized in Table 1. Three parameters – population of the sample, ratio of immunized individuals and reproduction rate of the virus – were set to different values. The effect of these adjustments was investigated and changes in the number of measles cases and timescale of the epidemic were observed.

Table 1. SEIR model results for the 2017 measles epidemic in Makó, Hungary

Population of the sample (N)	Ratio of immunised (%)	Total number of measles cases	Duration of epidemic
		$R_0 = 18$	
1000	90	73	6 months
400	90	29	4 months
400	80	78	3 months
150	80	29	2.5 months
		$R_0 = 12$	
1000	90	2	6 days
400	90	2	6 days
400	80	70	4 months
150	80	26	3 months
Empirical values			
?	90	29	2 months

At $R_0=18$ and N = 1000, assuming 90% effective vaccination, 100 susceptible individuals can be found in the population. The model estimates a total number of infected persons at 74 and the duration of the epidemic at half a year, which is more than double of the real values. By setting the population at N = 400, 30 infected individuals and 4 months were given by the model. This way the number of infected persons corresponds to the actual clinical data, but the duration is still longer compared to empirical findings.

Timescale of the epidemic can be compressed by increasing the proportion of susceptible people. If the vaccination coverage rate is changed from 90% to 80%, the duration of the epidemic is reduced to 3 months, but the total number of infected individuals becomes higher. Based on this anomaly, it can be presumed that the total number of involved population might be even lower than 400. Unfortunately, the results of the contact tracing procedure were not available for a better approximation.

An acceptable correspondence between the model calculations and the clinical data was observed by assuming N = 150 and 80% of vaccination coverage as input parameters.

The results – 30 infections in a two-month period – are close to the official values. For a better comparison, modelling with $R_0=12$ was also performed. The less contagious the virus, the fewer cases are found. Using this lower reproduction rate, only isolated cases can occur at 90% of vaccination coverage (which is a value that resembles the HIT). By decreasing the vaccination rate, the number of cases increases and the timescale is shortened, similarly to previous test examples.

Discussion

MMR vaccination in Hungary

In Hungary, MMR vaccine is mandatory. A single-dose, live-virus combined measles-mumps-rubella (MMR) vaccine is used to vaccinate infants of ≥15 months of age. A reminder vaccine is given to sixth year primary school students (~11 years of age). PRIORIX (GSK), PRIORIX-TETRA (GSK), ProQuad (MERCK) and the M-M-RVAXPRO (MSD Pharma) vaccines are currently used in Hungary for vaccination of children (at 15 months and 11 years of age) and for adults (62). The vaccines contain live attenuated viruses (26). Regarding insufficient cumulative anti-measles seropositivity levels, we would like to emphasize that potential gaps in the population-level humoral immunity (IgG) are attributable to early vaccination periods and are not a general phenomenon relative to the current immunization practices. The susceptibility of certain cohorts is likely attributable to the thermal instability of the historical Leningrad-16 vaccine, inefficient seroconversion owing to vaccination at a premature age (e.g. 9 months of age) and the questionable efficiency of the inoculum itself (9, 11, 25, 29, 30, 31). The 2017 measles outbreak in Makó was provoked by imported cases. Some of our bordering countries are still endemic for measles (27–30). Supplementary Figure 1 shows the European measles cases in the time period relative to the epidemics in Makó and Szeged. COVID-19 is increasing the risk of measles outbreaks. According to CDC Global Measles Outbreak reports of January 2021, 41 countries may postpone their measles campaigns for 2020 or 2021 due to the COVID-19 pandemic. This increases the risk of bigger outbreaks around the world (31).
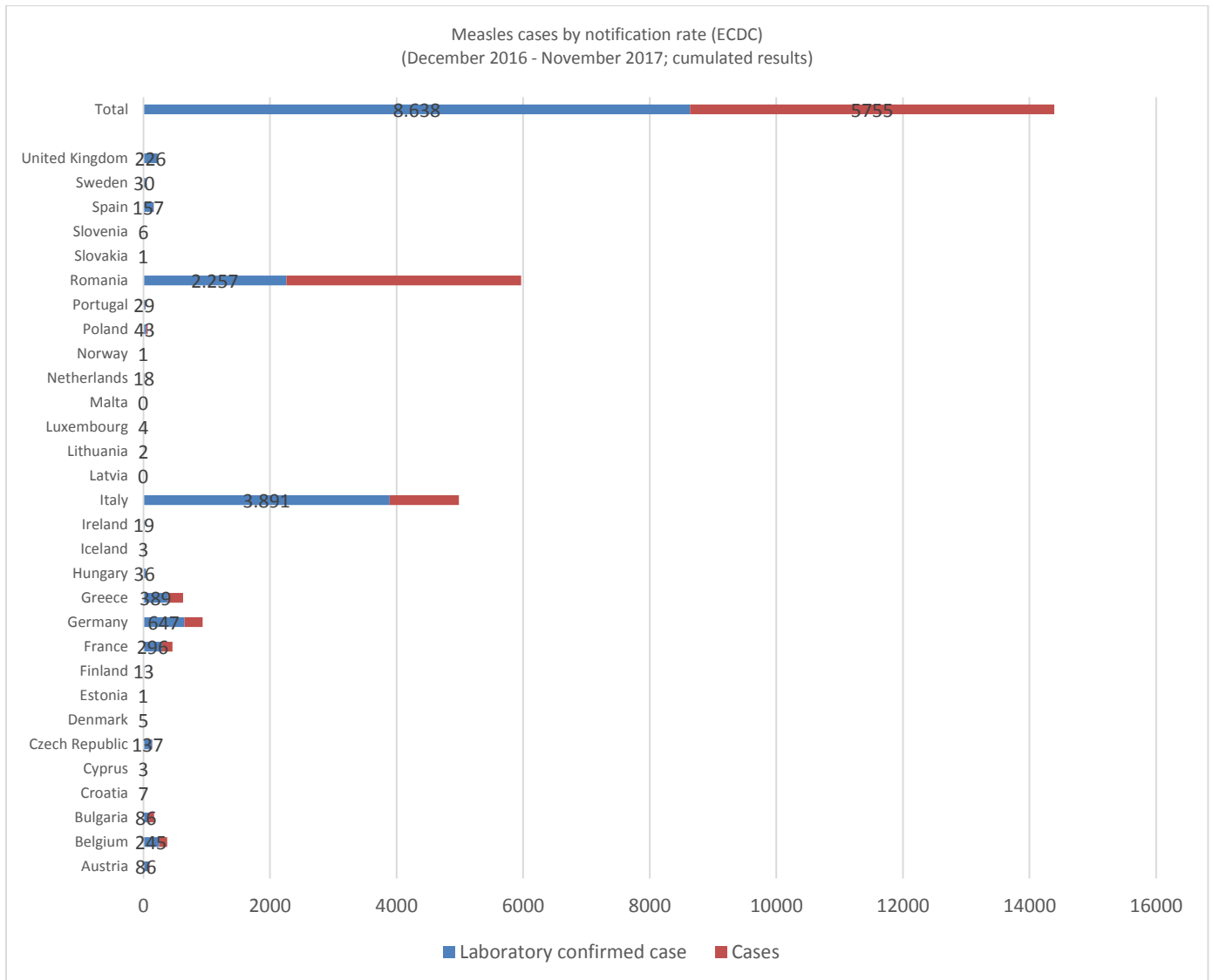
Supplementary Figure 1. European measles cases in the time period relative to the epidemics in Makó and Szeged (ecdc.europa.eu)

Between December 2016 and November 2017, numerous measles cases occurred in Europe, most of which were reported by Romania, one of Hungary's neighbouring countries. Source of data: https://www.ecdc.europa.eu/

2017 measles epidemic in Hungary

In 2017, according to the data of the national authorities, a total of 76 persons were infected with measles (corrected to 73 laboratory confirmed cases by ECDC Surveillance reports). The outbreak in the hospital of the small town of Makó involved 29 individuals and lasted from January 2017 to March 2017 (32,33). In order to demonstrate the spread of virus in a well-immunized population, where despite good vaccination coverage, latent immunization gaps (unprotected, seronegative cohorts) are present,

we used an open-source epidemiological report of the Hungarian National Public Health and Medical Officer Service (ANTSZ) (17 March 2017): 'At the peak of the Hungarian measles epidemics during the spring of 2017, 52 cases with measles-specific symptoms were reported. Of these, 15 laboratory confirmed cases (National Reference Laboratory for Measles and Rubella, National Public Health Institute, Budapest, Hungary) were registered by 16 March. Of these patients, 12 were health care workers (HCWs) and two were hospitalized patients. One of them was a foreigner, while the

other one was a patient living in the vicinity of a HCW. The epidemic affected two health care institutions, the Hospital of Makó and the clinics of the University of Szeged. The first measles case was imported in mid-February 2017 to the Hospital of Makó. The epidemic affected the hospital staff and their contacts. By 17 March, a measles infection was confirmed in case of a patient who was presumed to be the original importer of the virus, in case of 11 HCWs and in case of one of the HCW's contacts. At the time of this report, additional 11 cases (of which seven HCWs and three patients' contacts) were still under investigation. At the clinics of the University of Szeged, two persons – a HCW and a patient – fell ill with measles. Another 11 persons (six patients and five HCWs) were also suspected at the time of the report. Following the appearance of the abovementioned measles cases, in Csongrád County, a total of 391 people were vaccinated against measles, mumps and rubella (MMR). As the first cases of this period had been revealed, the National Chief Physician ordered strict monitoring and reporting of suspected measles virus infections. Thus, another 15 suspected cases were registered in several other counties. At the time of the report, laboratory testing was still ongoing (12)'.

The second group of imported cases was detected at the end of July 2017 in Nyíregyháza, Szabolcs-Szatmár-Bereg County, Hungary (11). Six unvaccinated Romanian children were hospitalised with clinical symptoms of measles. These cases were later laboratory confirmed (National Reference Laboratory for Measles and Rubella, National Public Health Institute, Budapest, Hungary). The subsequent disease spread among two additional HCWs (also laboratory confirmed) supports the susceptibility of certain clusters in the Hungarian population (11).

Epidemiological model- a didactic representation

In this section, we explain the spreading mechanism of infectious diseases for those who are not familiar with the computational background of modelling. To understand the basics of epidemic models, a simplified mathematical interpretation can be used. The spread of a disease can be described by S-shaped sigmoid mathematical functions, similar to the well-known pH titration curve, or haemoglobin saturation curves. As infectious diseases spread from human to human, the number of susceptible persons is decreasing over time and it influences the propagation of the pathogenic agent. In the beginning of the outbreak, the damping effect of recovered patients is minimal; the curve is very close to exponential and the number of new cases increases rapidly. At a certain time, a kind of equilibrium follows, daily recoveries can balance new infections and the curve reaches its inflection point. Afterwards, in the saturation phase, the epidemic slows down and at the end, no new cases are found and the vast majority of the population has recovered (Figure 4). The curves represented in Figure 4 are a graphic interpretation of a commonly used method for epidemic modelling – the compartment model. In this model, the population is divided into compartments – well-defined categories based on their epidemiological properties. In a compartment, all individuals behave exactly the same, e.g. they are all infected, all vaccinated, all exposed, etc. The simplest among these compartment models is the SIR model, where the letters of the acronym stand for susceptible, infectious and recovered.
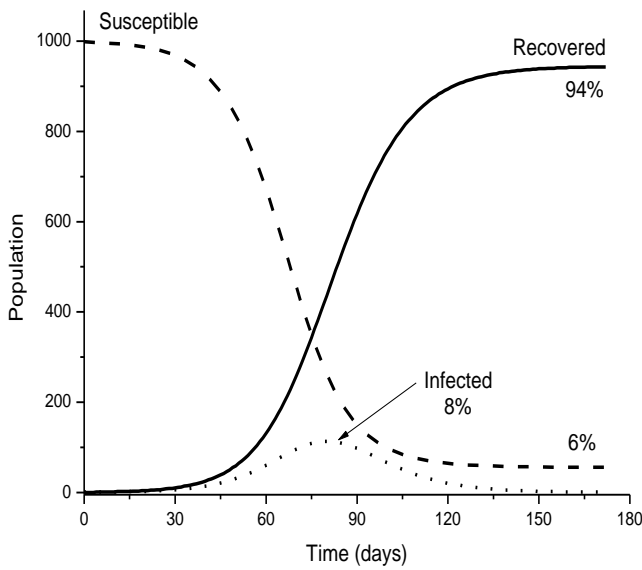
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Figure 4. SIR model curves of a hypothetical epidemic

As the disease spreads, the number of susceptible individuals decreases. First they get infected (I), but later on they will progress to the recovered compartment (R). Approximately 6% of the population managed to avoid contact with infected individuals. The peak of infections could be observed almost three months after the first case was recorded, affecting 8% of the population at the same time.

The progression of an individual in this model is easy to follow, each member of the population progresses from susceptible to infectious to recovered.

$$S \xrightarrow{\beta} I \xrightarrow{\gamma} R \ (1)$$

Transition between compartments is described by transition rates. Infection rate () represents the probability of transmitting the disease between a susceptible and an infectious person. In other words, the value of shows the number of individuals to whom an infectious person can pass the disease per day (18,39,40) For example, if the infection rate is 0.2, it will take five days on average to infect someone. If we assume that the patient is contagious for 10 days, two new infections are expected in this case.

The overall efficacy of the epidemic can be described by the number of these secondary infections originated from the primary infection, our first patient. This important parameter is the

basic reproduction number (R0). Each virus has its own average R0 value – 12-18 for measles and 3.3-5.7 for COVID-19, according to the literature.

The recovery rate (describes the probability of transition into the recovered compartment. For instance, if this rate is 0.1, the contagious period will last for 10 days.

From a mathematical perspective, the transitions can be described by the following differential equations, where S, I and R are the number of individuals in the corresponding compartments, while N is the whole population.

$$\frac{dS}{dt} = -\frac{\beta IS}{N} \ (2)$$

$$\frac{dI}{dt} = \frac{\beta IS}{N} - \gamma I (3)$$

$$\frac{dR}{dt} = \gamma I (4)$$

Mathematical methods (such as the Runge-Kutta method) are available for solving similar equations, but there is a simpler option. Using the built-in features of Microsoft Excel (or any equivalent spreadsheet application), it is possible to make calculations using an iterative method. Instead of solving the equations, the computer performs calculations that follow the daily changes in different compartments.

For modelling, and R0 have to be defined. Based on the definition of the transition rates, it can be seen that the recovery rate can be determined by the number of contagious days (T_cont).

$$\gamma = \frac{1}{T_{cont}} \ (5)$$

The basic reproduction number can be given as follows:

$$R_0 = \frac{\beta}{\gamma} \qquad (6)$$

Let us assume that in a certain population measles can be transmitted from a single person to 12 others (R_0=12) and they stay contagious for 6 days (T_cont=6). In this case:

$$\gamma = \frac{1}{T_{cont}} = \frac{1}{6} \text{ (7)}$$

$$\beta = R_0\gamma = 2 \text{ (8)}$$

Incubation time plays an important role in the spread of a disease. In a more sophisticated model (SEIR model), this can also be taken into consideration. A new compartment for the exposed part of the population can be generated. The susceptible person first gets exposed and will progress to the infectious state only after a certain time.

$$S \overset{\beta}{\Rightarrow} E \overset{\alpha}{\Rightarrow} I \overset{\gamma}{\Rightarrow} R \text{ (9)}$$

The parameter ' α ' is a new transition rate, which can be determined by the incubation time (T_inc) , similarly to γ :

$$\alpha = \frac{1}{T_{inc}}$$

New compartments can be added to the model anytime, such as the compartment M for individuals with maternal immunity or the compartment E for exposed individuals, who are already infected, but not infectious. Based on the characteristics of certain infectious diseases, further models have been developed, such as the SIS, MSIR, SEIR, SEIS, MSEIR and MSEIRS models. The second 'S' in the acronym indicates that after the infection, no permanent immunity can be reached and the individuals step to the S compartment again. In other models, the ratio of hospitalization, the ratio of mild and severe cases and epidemiological interventions can be included, with a more complex mathematical background.

In the examples described above some important parameters are simply disregarded, although it is possible to perform a more detailed computation. Vital dynamics, the natural dynamics of birth and death, can be included by adding two further parameters.

It is necessary to mention that compartment models have their well-known limitations and shortcomings. For instance, all individuals in the population are assumed to have an equal probability of coming in contact with others,

although society is inhomogeneous from the perspective of social distancing. Another drawback is that the traditional compartment model cannot handle uncertainty in model parameters. Working with a smaller set of data increases this uncertainty, making predictions unreliable. To overcome this problem, it is usual to calculate the SIR model over a few possible values for each parameter. A more complex solution is to use distribution functions instead of single numbers and if real-time data is available (e.g. we are in the middle of a pandemic), a clinical dataset can be utilized to adjust these parameters (36–38).

Regarding the SEIR model resembling the 2017 measles outbreak in Makó (Figure 4), we would like to note that both the simplified mathematical method and the input data were unreliable. With more sophisticated models, many different parameters can be taken into consideration (37,39). Despite that fact, the calculated values correspond in order of magnitude to the available data on the epidemic and support the experimental results describing the vaccination gap.

Model curves using a lower percentage of the population-level anti-measles protection rate are more fitting. This finding may indicate an even lower percentage of effectively vaccinated population than it was found previously (~90%).

It is concluded that the importance of seroepidemiological surveys is confirmed by the recent outbreaks of measles, mumps and rubella infections in several countries (14,16,17,40–45). Considering the HIT values, suboptimal anti-measles seropositivity ratios were detected in certain clusters of the early vaccination era (78.48% of sufficient anti-measles IgG antibody titres among individuals vaccinated between 1978 and 1987). This finding, which is in accordance with a recent study published by our colleagues (11) and historical literature data (46), suggests the existence of age-specific immunization gaps in the Hungarian population. For mumps and rubella, our preliminary data shows satisfactory immunity levels. Nowadays, in our country, the MMR vaccination coverage is ideal due to the

mandatory administration of safe and modern trivalent vaccines. Nevertheless, dubious immunization practices in some of our neighboring countries, aggravated by the detrimental effect of the COVID-19 pandemic and subsequent suspension of measles vaccination campaigns, may facilitate the occurrence of minor importation-related MeV outbreaks in susceptible cohorts. Using the example of the 2017 measles outbreak in Makó, it has been demonstrated that in possession of key epidemiological parameters (e.g. R0 value, estimated vaccination coverage of a given population, number of infected and recovered individuals, duration, etc.), a simple SEIR model can give a good approximation regarding the course of an infection.

We believe that awareness may significantly reduce the extent of an epidemic (38,47). In the light of current disquieting epidemiological circumstances, we suggest the introduction of open-access mathematical and epidemiological models into modern natural science education of students. Today, online epidemic models are easily available for the public (35,36). Practical introduction to these plain calculation models could help students understand the rationale behind epidemiological data. We believe that a practical demonstration of epidemiological events can promote a better understanding of countermeasures and also allow for an easier adaptation to the current epidemiological regulations.

Limitations of experimental work

The diagnostic ability of our assay was calculated based on the results obtained by well-established kits capable of humoral antibody detection, rather than on neutralizing antibody titres that could serve as an absolute correlate of protection (48–50). It is important to emphasize that immunity to measles is a

complex orchestration between the cellular and humoral immunity. For this reason, only antibody-based definitions of vaccine success and failure may be misleading, or at least simplistic and incomplete (51).

Limitations of mathematical modelling

Input data plays a key role in modelling of epidemics. Even when the number of cases is high – like in the 2020 COVID outbreak – the confidence of fitting is poor at the beginning of new cases vs. time graph. The first cases are usually unexpected, quarantine and social distancing protocols are not applied yet and if the disease has a low prevalence in the population, the accuracy of the diagnosis might be low. Besides that, atypical symptoms can be misleading for physicians. Furthermore, statistical values, such as basic reproduction number, incubation and recovery time, depend on other factors, such as social distancing and the health care system.

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