Supplementary Online Content

Lo NC, Hotez PJ. Public health and economic consequences of vaccine hesitancy for measles in the United States. *JAMA Pediatr*. Published online July 24, 2017. doi:10.1001/jamapediatrics.2017.1695

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. Additional Description of the Methodology

In this supplement, we provide additional description of the methodology used to estimate the public health and economic impact of measles under increasing vaccine hesitancy.

Statistical model and analysis

We adapted a stochastic mathematical model to estimate the probability mass function for the size of an measles outbreak in children following introduction of an imported case.[1] The model applies a simple random walk to estimate the probability of new cases based upon the effective reproductive number (R). The effective reproductive number is computed (see equation 1) using the basic reproductive number (R_0) for measles and proportion of children that are immune (c; vaccine coverage, assuming 95% efficacy of vaccine).

$$R = R_0(1 - C * 0.95) \quad (eqn\ 1)$$

Thus, the effective reproductive number is a function of vaccine coverage within a homogenous zone.[1] The probability of an infected person causing a new case is modeled as R/(1+R) in the simple random walk. We computed the probability (q) of an outbreak of size 'x' (equation 2) using a probability mass function model for an infectious disease outbreak in a highly immunized population (i.e., no population-wide outbreaks). We conservatively modeled a maximum outbreak size of 100 based on empirical data of outbreak size from highly immunized population in the United States and United Kingdom.[1,2]

$$q(x) = \frac{R^{x-1}}{(R+1)^{2x-1}} \frac{(2x-2)!}{x!(x-1)!} \ (eqn\ 2)$$

We weighted the probability of introduction by the state's population, where more populated states had a higher probability of receiving an imported measles case. This was supported by our analysis that found a high correlation coefficient (0.8) for the relationship between states' annual number of imported cases and population size.

We estimated annual measles cases in the United States and associated societal costs by running the model 10,000 times and reporting the median and 5th and 95th percentiles (90% prediction interval). The range of annual measles cases in recent years informed the choice for interval size. The model was coded in R (R Foundation for Statistical Computing; Vienna, Austria).

We performed a number of one-way sensitivity analyses (see Methods). We modeled an expanded age group (ages 0-11), which added children ages 0-2 years. In this model variation, we assumed maternal immunity for children during the first 6 months of life, 6-12 months as fully susceptible, and estimated a linear increase during the first dose of MMR vaccine 12-15 months comparable to vaccination coverage at 2 years. We also tested a slow phase-in of vaccine hesitancy. In this analysis, we applied a 5% reduction in vaccine coverage in the youngest age group (age 2) for each year over a 10-year time period, and computed measles cases and costs over this time period.

We did not discount costs in the base case analysis since the calculation was made for a hypothetical reduction in vaccine coverage in present day over a one-year time horizon. However, we did apply a 3% annual discount rate in the sensitivity analysis that computed costs over a 10-year time period with slow phase-in of vaccine hesitancy. We sourced public sector costs per measles case from literature, and adjusted to 2016 US$ with the Consumer Price Index; we approximated an average cost per measles case for the base case analysis and used the broad range from the literature to inform the interval for the sensitivity analysis.

Calibration and Validation

For the calibration procedure (see Methods), we implemented a general-purpose optimizer with the Nelder-Mead algorithm ("optim" function in R) for minimization of a sum of least squares loss function. Since this algorithm solves a local optimum, we initiated the search at multiple points to find the global optimum.

For validation, we used an independent dataset on national MMR vaccine coverage and annual incidence from the England and Wales to test the model in a highly immunized population.[1] This data provided a historical record of national vaccine coverage (varying over time from 92% to 85% during 1995-2002), annual measles incidence, and number of outbreaks. We chose to analyze model validity on this United Kingdom dataset based on availability of this independent dataset and similarity of this highly immunized population to the United States. For the validation process, we first calibrated the model to the period of stable vaccine coverage (1995-1998; 92.7% vaccine coverage assuming county-level variance comparable to that of the United States). Once the model was calibrated, we then predicted over the period of 1999-2002 when vaccine coverage declined from 91.8% to 84%. We found that the model prediction for rise in measles incidence with declining vaccine coverage captured the observed data from the UK given the stochastic nature of measles outbreaks and wide prediction intervals (eTable 1), which improves our confidence in the predictive power of the model.

eReferences

1. Jansen VA, Stollenwerk N, Jensen HJ, Ramsay ME, Edmunds WJ, Rhodes CJ. Measles outbreaks in a population with declining vaccine uptake. *Science* 2003; **301**: 804.

2. Measles- United States Morbidity and Mortality Weekly Report (MMWR). ; 2010-2015.

3. Measles- United States Morbidity and Mortality Weekly Report (MMWR), 2010-2015.

© 2017 American Medical Association. All rights reserved.

eTable 1. Model Calibration in United States and Validation in England and Wales

Description	**Vaccine coverage**	**Model prediction (90% PI)**	**Observed**
Calibration in United States, 2015-16			
Annual measles cases in children	92.7%	48 (25-139)	48
No. outbreaks, annual	92.7%	4	4
Calibration in England and Wales, 1995-1998			
Annual measles cases	91.8%	28 (13-96)	27 (9-65)*
No. outbreaks, annual	91.8%	3	4
Validation in England and Wales, 1999-2002			
Annual measles cases, 1999	88.5%	49 (15-178)	84
Annual measles cases, 2000	87.9%	56 (16-201)	63
Annual measles cases, 2001	87%	75 (17-226)	145
Annual measles cases, 2002	84%	143 (21-341)	150

Note: Outbreak defined as chain of transmission of 3 or more.

*Range of annual incidences in recent years to calibration period.

90% PI; prediction interval

© 2017 American Medical Association. All rights reserved.

eTable 2. Number of Annual Measles Cases in the United States for the Overall Population and Children

Year	**Cases, population**	**Estimated cases, children (2-11 years)**
2010	63	18
2011	220	62
2012	55	15
2013	187	52
2014[a]	667	187
2015	188	53
2016[b]	70	20

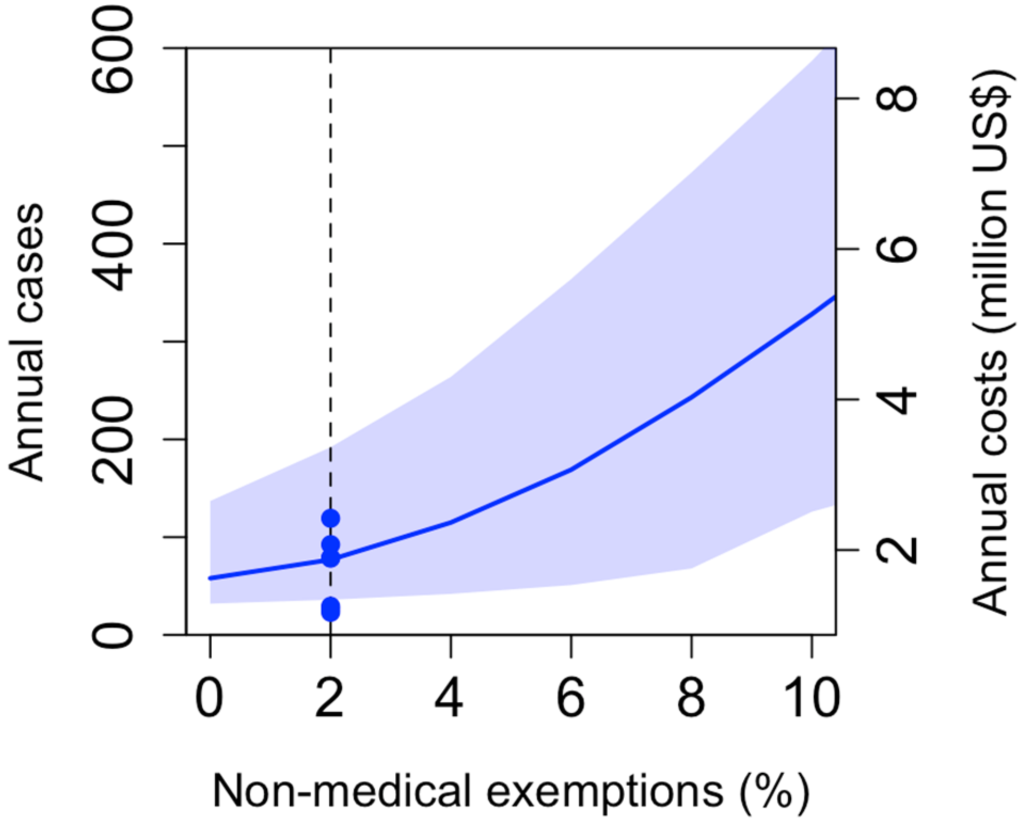
Source: U.S. Centers for Disease Control and Prevention, accessed 2/9/17. We estimated 28% of cases are in children (ages 2-11) based on CDC reports.[3]

[a] In 2014, a single outbreak in an Amish population caused 383 cases.

[b] Preliminary data, subject to change.

© 2017 American Medical Association. All rights reserved.

eFigure. Public Health Impact and Public Sector Costs of Childhood Measles in the United States With Increasing Prevalence of Vaccine Hesitancy in Expanded Age Group (Ages 0-11 Years).



We used county and state-level data on MMR vaccine coverage in children (ages 0-11) in the United States, and applied a stochastic mathematical model that related vaccine coverage with probability and size of an outbreak in children. We computed the median annual cases in children from the United States (left y-axis) and associated public sector costs (right y-axis) and associated 90% prediction interval (shaded) across a range of prevalences for non-medical exemptions (i.e., vaccine hesitancy). We computed annual cases in children for the present day based upon the current prevalence of vaccine hesitancy (2%) shown in vertical dashed line. The blue points represent the number of annual measles cases in recent years at the current prevalence of vaccine hesitancy, and demonstrate the stochastic nature of measles outbreaks. We estimated the effects of increasing national vaccine hesitancy to 10% prevalence, and the removal of non-medical exemptions (0% prevalence of vaccine hesitancy). This model provides a sensitivity analysis on the effect of age group on the main analysis (Figure 1).

© 2017 American Medical Association. All rights reserved.