The basic reproduction number (R_0) of measles: a systematic review

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The basic reproduction number, R nought (R_0), is defined as the average number of secondary cases of an infectious disease arising from a typical case in a totally susceptible population, and can be estimated in populations if pre-existing immunity can be accounted for in the calculation. R_0 determines the herd immunity threshold and therefore the immunisation coverage required to achieve elimination of an infectious disease. As R_0 increases, higher immunisation coverage is required to achieve herd immunity. In July, 2010, a panel of experts convened by WHO concluded that measles can and should be eradicated. Despite the existence of an effective vaccine, regions have had varying success in measles control, in part because measles is one of the most contagious infections. For measles, R_0 is often cited to be 12–18, which means that each person with measles would, on average, infect 12–18 other people in a totally susceptible population. We did a systematic review to find studies reporting rigorous estimates and determinants of measles R_0. Studies were included if they were a primary source of R_0, addressed pre-existing immunity, and accounted for pre-existing immunity in their calculation of R_0. A search of key databases was done in January, 2015, and repeated in November, 2016, and yielded 10 883 unique citations. After screening for relevancy and quality, 18 studies met inclusion criteria, providing 58 R_0 estimates. We calculated median measles R_0 values stratified by key covariates. We found that R_0 estimates vary more than the often cited range of 12–18. Our results highlight the importance of countries calculating R_0 using locally derived data or, if this is not possible, using parameter estimates from similar settings. Additional data and agreed review methods are needed to strengthen the evidence base for measles elimination modelling.

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Introduction

In the pre-vaccine era, measles was amongst the most severe childhood illnesses, contributing to very high morbidity and mortality, with complications including pneumonia, diarrhoea, dysentery, and blindness.[1] The introduction of the measles vaccine in the mid-1960s substantially reduced mortality; however, regions have had varying success in measles control, and morbidity and mortality is still high worldwide despite the existence of an effective vaccine.[2,3] In July, 2010, WHO convened a panel of experts that concluded that measles can and should be eradicated.[4] As one of the most contagious infections, however, measles elimination relies on exceptionally high levels of immunity in the population.

Measles elimination programmes can benefit from application of the epidemiological concept of the basic reproduction number, R nought (R_0). R_0 is defined as the average number of secondary cases generated by a primary case in a completely susceptible population.[5] Although R_0 is sometimes referred to as if it is a fixed biological characteristic, it is in fact an epidemiological summary measure of biological and sociodemographical variables providing a threshold parameter for the spread of disease, without units. Determinants of R_0 include the probability of transmission between an infectious individual and a susceptible individual, the type and frequency of contacts between individuals, and the duration of infectivity:

$$R_0 = \beta cD$$

where β is the probability of transmission, c is the number of contacts, and D is the duration of infectivity. The effective reproduction number, R_e, refers to the average number of people infected by each case in a population that has some level of immunity and is dependent on and related to R_0 in its simplest form through the proportion of the population that is immune. When R_e is greater than 1, each infected individual transmits the disease to more than one person, and a disease can propagate in a population. If R_e is less than 1, not every case will result in a new infection in another individual, and transmission will cease (small chains of transmission can occur, however). The critical proportion of immune individuals that is needed to interrupt transmission in a population, also known as the herd-immunity threshold, can be used as a target for immunisation programmes to stop the spread of disease.[6] Generally, this is accepted to be the solution of the following equation:

$$p = (1 - 1/R_0)$$

where p is the fraction of the population that is immune. Considering the relationship between R_0 and immunisation coverage to achieve herd immunity (Eq 2, figure 1), accurate estimates of R_0 are necessary, as small differences in R_0 within the lower range can make a large difference to the level of vaccine coverage needed to achieve herd immunity, which is particularly pertinent to measles. Although R_0 is known to be context-dependent, public health researchers frequently use the measles R_0 range 12–18 reported by Anderson and May.[7,8] The primary objectives of this systematic review were to summarise measles R_0 estimates and identify key covariates of R_0 to improve understanding of the herd immunity threshold and immunisation coverage required for measles elimination.

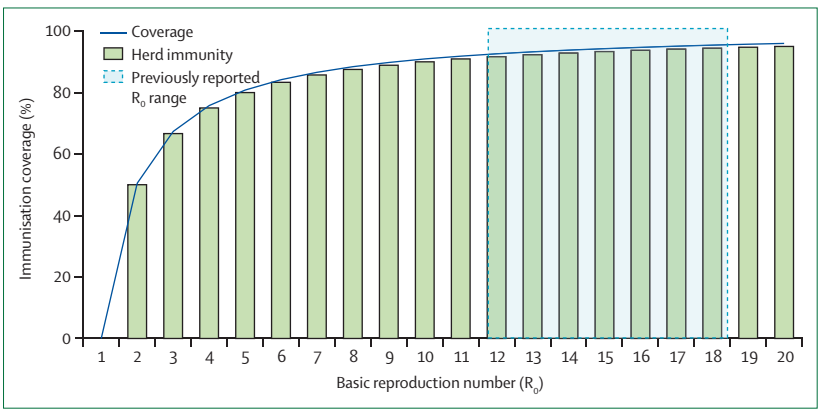

***Figure 1*: Measles basic reproduction number (R_0), herd immunity, and coverage**
As R_0 increases, higher immunisation coverage is needed to achieve herd immunity. Blue zone indicates the R_0 estimate of 12–18.[7]

Methods

Search strategy and selection criteria

Two of the authors (FMG, GL) used a participants, interventions, comparisons, outcomes (PICO) strategy to identify key words to generate a highly sensitive search strategy in consultation with a librarian, with review by a second librarian. On Jan 29, 2015, and July 24, 2015, the search strategy was applied in MEDLINE, Embase, and Global Health databases (appendix pp 1–7). The search was restricted to articles written in English. We included non-research articles such as letters, commentaries, and conference abstracts. Duplicates were removed before applying selection criteria. Inclusion criteria were publications that were a primary source of R_0 and addressed pre-existing immunity and accounted for it in their calculation of R_0. Studies were excluded if they were not about measles, if they reported R_e instead of R_0, if they used simulated data to calculate R_0, if they were not a primary source of the reported R_0 estimate, if there were insufficient data to ensure inclusion criteria were met, if the report was not written in English, or if the publication was inaccessible.

See Online for appendix

We applied four levels of screening to identify publications reporting a primary estimate of R_0 before the quality appraisal. The first level of screening was completed by GL or FMG and involved searching the titles and abstracts for the term "measles" and at least one of the following: "reproduction number", "reproductive number", "outbreak", "elimination", "surveillance", "transmission", "modeling", "imported cases", or "importations". The second level of screening was completed by GL and involved searching the full text for the terms "reproductive number" or "reproduction number". The third level of screening was completed by FMG and GL in parallel and involved reading the full text. Discrepancies were resolved through discussion and consultation with NSC. While reading the full-text publications, references identified as potentially relevant were retrieved and subject to the third level of screening. The fourth level of screening was conducted by JH, who screened the full text of the articles that passed the third level of screening.

We repeated the search on Nov 28, 2016, limiting the search to papers that were published between Jan 1, 2015, and Nov 28, 2016. We compared the results to the outcome of the search completed on July 24, 2015, to identify and remove duplicates. We subjected the resulting publications to the four levels of screening, but modified level 1 screening such that FMG screened titles and abstracts and selected any that were likely to report R_0 on the basis of experience with the previous screening strategy, rather than using key term criteria. Results for the initial and updated search are reported together.

Data abstraction and quality assessment

Data abstraction was completed in parallel by SB and FMG, and the results were reviewed by JH. Abstracted variables included study period, vaccine era (pre-era or post-era), setting, type of data, method of calculation, population immunity, and R_0 values or range. Corresponding authors were contacted if required to clarify details in their publications. The variability in study methods presented a challenge when selecting a quality-appraisal tool. We selected the STROBE reporting checklist as the basis for our quality appraisal and annotated the checklist with examples relevant to our subject matter and supplementary questions from the Meta Quality Appraisal Tool (MetaQAT; appendix pp 8–12).[9] MetaQAT questions about potential bias served as prompts to assess the internal and external validity of the studies. Because of the relatively small number of studies reporting R_0, the variability of the methods used, and a lack of consensus on best methods in the research field, if the quality of reporting was low but the article was not methodologically flawed, it was included. The quality assessment was completed by SB and FMG in parallel and is reported in table 1. Discrepancies were resolved through discussion and consultation with JH, NSC, and SLD.

Principle summary measures and synthesis

The high level of heterogeneity between the studies in terms of setting and methodology meant that performing a meta-analysis on the combined R_0 values would not have been informative and would have limited applicability. The median, however, was used to obtain the midpoint of reported R_0 values stratified by covariates including type of data used to estimate R_0, measles vaccine eras, WHO region, country development status, population density, and birth rate. Country economies were categorised as least developed or developing if they met the UN classification criteria for least developed countries[29] or if they did not meet the criteria but were different from the remaining developed countries in terms of human developement index and gross domestic product (eg, Kenya, India, and Cameroon).

	Years represented by data	Vaccine era*	Setting	Type of data	Method of R_0 calculation	R_0 range
Paterson et al (2013)[10]	1838, 1882	Pre	Two ships, sailing from Belfast and Plymouth to Sydney, Australia	Surveillance	R_0 was determined using the maximum likelihood of the entire outbreak (the product of the probabilities for each generation), p(infection) = 1 – (1 – (r_0/P)) [ci] and Reed-Frost stochastic model to determine when susceptible people would become infectious between time t and t + 1; used 1000 simulations	7·1–10·9
Becker et al 1998)[11]	1861	Pre	Hagelloch, Germany	Outbreak	$R_0 = \beta \times S0/\gamma$, where β is infection rate, S0 is susceptibles at the start of the epidemic, γ is removal rate	10·3–11·3
Merler et al (2014)[12]	1901–2009	Pre	Italy	Serological survey	$R_0 = \beta/\gamma$, where β is transmission rate, γ is infectious period; estimated from a dynamical system model; accounted for the reduction in susceptibles: $\beta(1-\varepsilon)(1-fv)$, where ε is birth rate, v=fraction of newborns vaccinated with vaccine efficacy f; accounted for the vaccinated in the transmission rate, and then used this transmission rate to calculate R_0	13·0
Metcalf et al (2009)[13]	1907–30	Pre	Copenhagen, Denmark	Surveillance	$R_0 = 1/(mu \times A)$ = birth rate/mean age of infection	8·3
Anderson and May (1982)[7]	1900s (1912–79)	Pre and post	England, Wales, North America	Unknown	$R_0 = N/Nt$ where N is size or density of host population and Nt is γ/β (immune capita rate divided by transmission coefficient); alternatively, $R_0 = 1 + L/A$,[14] where L is life expectancy, A is average age of infection; Eq 15 (used for 1956 and 1970 estimates)	12·5–18
Olsen et al (1988)[15]	1928–68	Pre	Copenhagen, Denmark	Surveillance	$R_0 = 1 + (L/A)$, where L is average life expectancy and A is average age at infection	15·4–17·0
Hooker et al (2011)[16]	1939–65	Pre	Ontario, Canada	Surveillance	From their model, $R_0 = \beta \times S0/\gamma$, but they report β/γ only, so S0 = 1, which is 100% of the population	27·0
Edmunds et al (2000)[17]	1970–90?	Pre	Select European countries	Serology and surveillance	R_0 was determined using age distribution and total population, using an eigenvector to determine the age distribution of the susceptible population	7·1–29·3
Wallinga et al (2001)[18]	1956–65, 1983–?	Pre and post	Western Europe	Serology and surveillance	$R_0 = r(K)$; next-generation method, using different mixing matrices and age structure; took into account the fraction susceptible by age	1·43–770·38
He et al (2010)[19]	1950–?	Pre and post	UK	Surveillance	$R_0 = \beta\text{-bar} \times IP$, where β-bar is the mean transmission rate and IP is the length of the infectious period	21·0–57·0
Szusz et al (2010)[20]	1969–2006	Pre and post	Niger, Senegal, Kenya, Tanzania, Zaire, Uganda, Cameroon, Zambia, and India	Serology and surveillance	$R_0 = G/(A-D)$, where G is inverse of per capita birth rate, A is age of infection, and D is average duration of maternal antibodies	3·7–203·3
Broutin et al (2005)[21]	1983–86 and 1987–2000	Post	Niakhar, Senegal	Surveillance	$R_0 = G/A$, where G is 1/per capita birth rate	4·6
Mossong et al (2000)[22]	1996	Post	Luxembourg	Outbreak	R_0 was estimated using final number of cases, number of susceptible people before epidemic, and total community size	6·2–7·7
Wallinga et al (2003)[23]	1999–2000; additional data 1976 onwards	Post	Netherlands	Serology and surveillance	R_0=Nt/St, where Nt is population size, St is number of susceptible people; used the geometric mean <Nt/St>, which is equivalent to R_0=1/Sc if the population mixing is homogeneous	23·0
Grais et al (2006)[24]	2003–04	Post	Niamey, Niger	Surveillance	Determined R_e, and then determined R_0 using $(1\text{-immune/N})R_0 = R_e$	4·7–15·7
van Boven et al (2010)[25]	2006	Post	North Rhine-Westphalia, Germany	Outbreak	$R_0 = Rp/(1-pVE)$, where pVE is the fraction immune; determined Rp first in the population that includes some immune individuals, then take out the fraction immune and get R_0; of the 1250 students, there was a considerable fraction where the vaccination status was unknown, so estimated these from the epidemic data; used Bayesian methods to determine this, and get a value for R_0	22·1–32·1
Glasser et al (2016)[26]	2008	Post	California, USA	Survey	R_0 was determined using next-generation matrices with school-specific contact rates to determine R_{0i} for each school, and is a weighted average; R_0 was estimated for a well mixed population assumption (10·7) and for a structured population (18·1)	10·7, 18·1
Plans (2012)[27] and Vivancos et al (2012)[28]	2012	Post	Merseyside, England	Outbreak	According to Plans,[27] Grais et al[24] estimated R_0 from the estimates of R derived by van Boven et al;[25] $R_0 = R/(1-VE)$, where VE is vaccine effectiveness	6·2–9·5

R_0=basic reproduction number. R_e=effective reproduction number. *Vaccine era was determined for each study individually, as year of measles vaccine introduction varied slightly country to country.

***Table 1*: Summary of reviewed studies**

Measles vaccine era was determined for each study individually as year of measles vaccine introduction varied slightly between countries. Population density was determined using World Bank data and official government websites or calculated using surface area and population estimates. Studies were grouped by population density using a cutpoint of 1000 people per km² (≥1000 people per km² was deemed high density, and <1000 people per km² was deemed low density) based on the distribution of the population densities in

For **World Bank population data** see http://data.worldbank.org/indicator/EN.POP.DNST?page=6

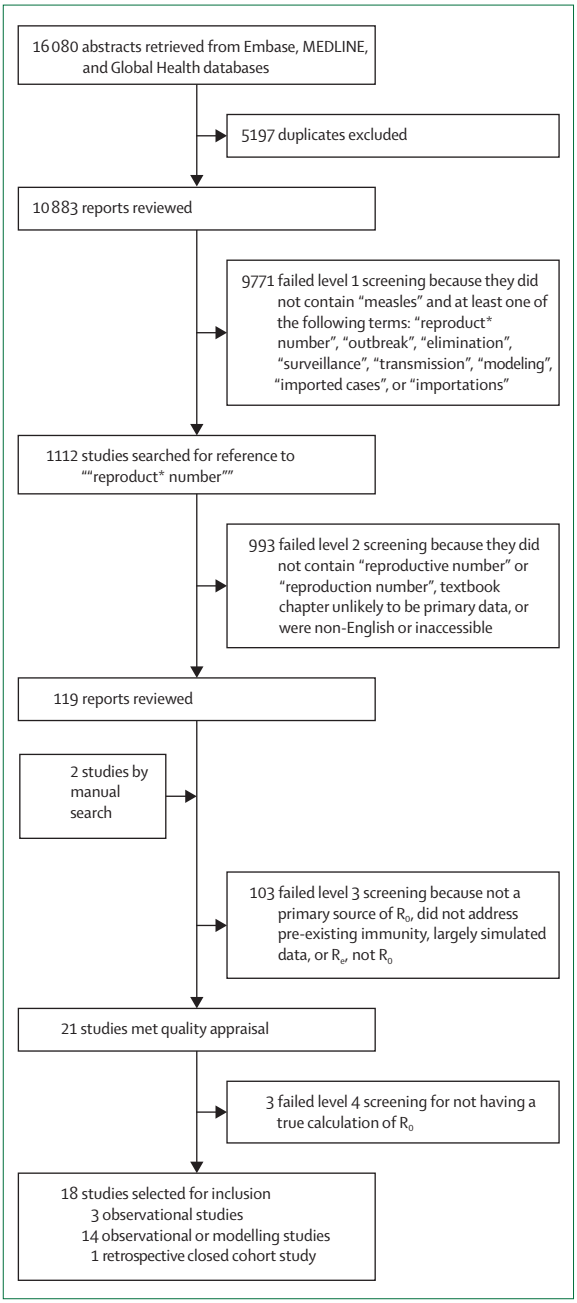

***Figure 2*: Flowchart**
"Reproduction*" indicates a word containing "reproduct-" and any suffix. R_0=basic reproduction number. R_e=effective reproduction number.

the studies. Studies were grouped by birth rate using a cutpoint of 20 births per 1000 population (≤20 births per 1000 population or >20 births per 1000 population). Studies were categorised as using surveillance or survey data (more than one location), combined seroprevalence with or without surveillance data, or outbreak data (one location). Pooled estimates are reported with the number of publications and the number of R_0 estimates. Excel spreadsheets were used to manage records and data throughout the review. This review conforms to PRISMA guidelines.

Results

We identified 16 080 studies, of which 5197 were duplicates, leaving 10 883 unique reports (figure 2). 1112 reports passed the level 1 screening, and 119 reports passed level 2 screening. 19 reports passed level 3 screening. Reasons for exclusion included reporting of R_e and not R_0, simulated data in the case of modelling studies, and insufficient data for abstraction. We retrieved two additional reports by hand-searching references, both of which passed level 3 screening, bringing the total to 21 reports. Full-text screening of the 21 reports by a third author with expertise in mathematical infectious disease modelling identified three of the studies as not reporting a true R_0. Thus we included 18 studies in this systematic review (table 1).[7,10–13,15–28] No studies were excluded on the basis of poor quality.

The study countries ranged from developed to least developed and included countries in North America, Europe, Africa, and Asia. Study periods ranged from 1838 to 2012. Seven studies used data collected before the introduction of a measles vaccine programme, seven studies used data from the measles vaccine era, and four studies used data from both eras. The study that reported ship travel log data from 1838 and 1882 for sea voyages from the UK to Australia is distinct from the others in its data source.[10] The 18 studies reported 58 R_0 estimates, ranging from 1·43 to 770·38 (figure 3, figure 4). Ten estimates were contained within the often cited range of 12–18; 16 estimates were above the 12–18 range; 27 estimates were below the range, and five estimates were reported by Anderson and May[7,8] and comprised the range (figure 3).

One study reported 20 R_0 values and an average R_0 based on settings within England during the same period.[19] We used the average R_0 for this study in the covariate analysis. Another study reported 11 R_0 values for India.[20] For the covariate analysis, the 11 values were pooled into two categories: urban or peri-urban and rural. Yet another study reported five R_0 estimates,[18] but two of these estimates were extreme values deemed feasible by the authors. These two values, 1·43 and 770·38, are featured in table 1 and figure 3, but were excluded from the analyses by covariates because they were hypothetical. One study reported six R_0 values,[17] three of which were country-specific and based on a default matrix, and three of which were based on pooled European parameters and default, diagonal, and proportionate mixing matrices. Since much of the covariate analysis relied on additional country-level data (eg, birth rate), the three country-specific R_0 values were used in the covariate analysis rather than the pooled estimates. For another study, we abstracted five R_0 estimates, three of which were Britain pre-1968 and were averaged to 15·9 for the covariate analysis, resulting in three R_0 estimates of 15·9, 12·8, and 12·5.[7]

R_0 estimates by method of calculation

Studies included in this literature review used diverse methods to calculate R_0, ranging from sophisticated statistical methods to very simple calculations using easily obtained demographical parameters (table 1). Although the method can affect the resulting value of R_0, different methods that produce similar values of R_0 can be quite informative. The same two measles outbreaks were analysed in more than one of the studies reviewed. R_0 estimates for a measles outbreak in Niamey, Niger were calculated in two studies.[20,24] One study reported R_0 9·6 using the equation $R_0 = G/(A-D)$, where G is the inverse per capita birth rate, A is the age of infection in years, and D is the average duration of maternal antibodies.[20] First determining an effective reproductive value, R_e, and then accounting for the fraction of the population conferring immunity, the other study determined R_0 for this same population to be 4·7–15·7 (median 10·2),[24] which includes the R_0 value as determined by the other study.[20] Two studies both determined an R_0 estimate for a measles outbreak in Niakhar, Senegal, reporting R_0 4·9 and R_0 4·6, respectively.[20,21] The only difference in the method of calculation was that one ignored the effects of maternal antibodies.[21]

R0 estimates by covariates

Stratifying R_0 estimates by the type of data used yielded median R_0 values of 13.2 and 16·1 for surveillance data and seroprevalence data with or without surveillance data, respectively, and 9·9 for outbreak data (table 2). Focusing on studies using pre-measles vaccine data, R_0 ranged from 6·1 to 27·0, with a median of 11·1. For studies using measles vaccine-era data, R_0 values ranged from 3·7 to 203·3, with a median R_0 of 15·7. The studies contained within each era, however, were highly heterogeneous in terms of setting, study period, and methods of estimation. Stratifying measles R_0 estimates by developed and least developed or developing countries, median measles R_0 was 12·9 in developed countries and 15·9 in least developed countries. As the least developed or developing country estimate contained only vaccine-era estimates that could have affected the R_0, we stratified country-development status by vaccine era. During the vaccine era the median measles R_0 in developed countries was 11·7; by contrast, median measles R_0 in least developed or developing countries during the vaccine era was 15·9. Stratifying measles R_0 estimates by WHO region, the measles R_0 median values were 15·3 in the Americas, 12·9 in Europe, 12·8 in Africa, and 16·4 in southeast Asia. In view of the relation between R_0 and the number of contacts in a population, we stratified measles R_0 estimates from WHO regions by population density. In Europe, Africa, and southeast Asia, there was a mix of high-density and low-density settings, and for each region the median measles R_0 was highest in the high-density settings. An overall comparison of high and low population-density settings yielded medians of 12·6 and 15·9 in low-density and high-density settings, respectively. Stratifying by birth rate, median measles R_0 was 10·4 in low birth-rate settings and 12·9 in high birth-rate settings.

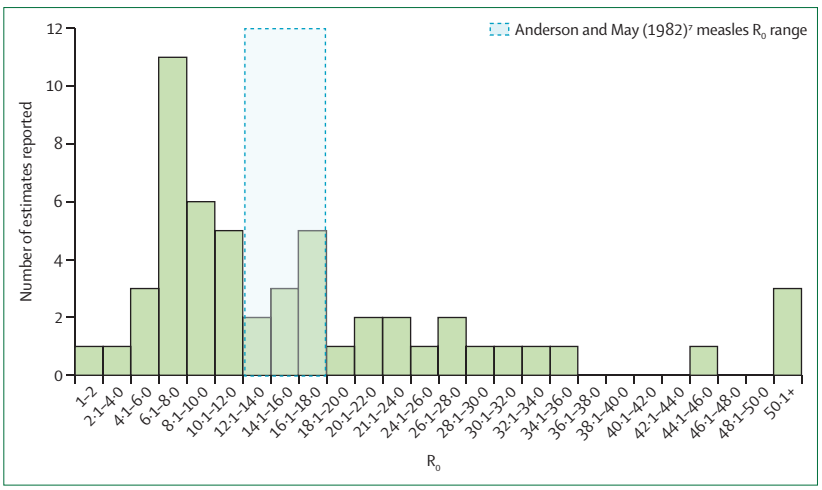

***Figure 3*: Reported R_0 estimates**
The 18 studies identified reported 58 R_0 estimates. R_0=basic reproduction number.

Discussion

R_0 is defined as the number of secondary cases of an infectious disease arising from a typical case in a totally susceptible population; however, it can be estimated in populations with pre-existing immunity if immunity can be accounted for in the calculation. Our summary of published measles R_0 estimates reveals a much wider range of values than the often cited 12–18 range.[7,8] Although we provide median estimates of measles R_0 for summary purposes, the data show that there are multiple setting-specific determinants of R_0 and therefore calculation of a local R_0 estimate is preferable to a reported average. Pooled estimates by key covariates highlight this point and provide insight into the relation between these covariates and R_0. Thus, similar to reviews of R_0 for other pathogens,[30–32] our data highlight that R_0 is not an intrinsic value characteristic of a given pathogen, but rather describes the transmissibility of that pathogen within the specific population and setting under study. R_0 depends on sociodemographically dependent variables and the biology of the infectious agent. The number of contacts, for example, can depend on population density, birth rate, cultural practices, or assumptions about contact rates when parameterising models. These covariates are often similar within a region but can vary across regions, underscoring the argument that R_0 is context-dependent. In addition, estimates of R_0 can be biased because of the data used to determine the final size of an outbreak and the average age of infection (eg, surveillance, serosurveys) and the quality of those data. The scientific literature we reviewed suggested that the likely determinants of R_0 include contact patterns (cultural practices, school calendars, public infrastructure), birth

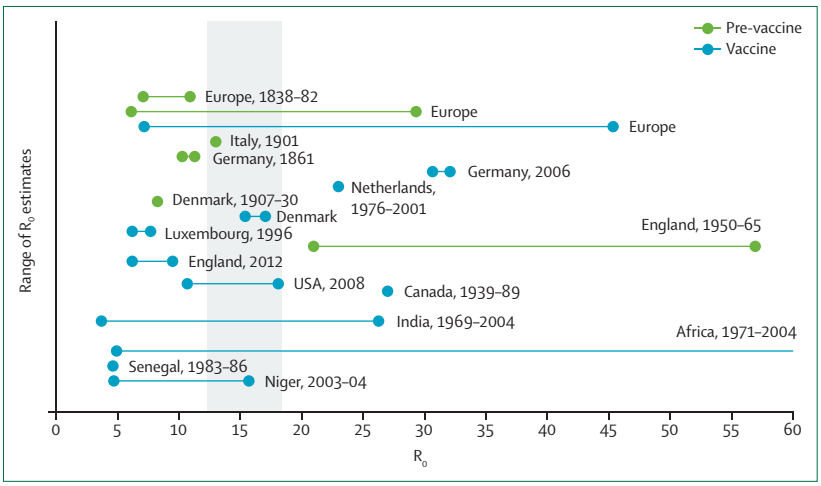

***Figure 4*: Measles R_0 estimates by geographical location and time**
Excludes feasible estimates of 1·43 and 770·38 from Wallinga et al (2001).[18] For data from Szusz et al (2010),[20] we plotted one range for India and one range for Africa. R_0=basic reproduction number.

rate, disease control measures including hygiene (infection prevention and control), waning immunity, nutrition, surveillance (data quality, asymptomatic or mild cases), and population density. Our covariate analyses attempted to address some of these determinants.

Median measles R_0 was higher in the vaccine era than the pre-vaccine era. This was unexpected given that vaccination should reduce the size of the susceptible population, which can reduce R_0. One possible explanation might be that all the studies in the pre-vaccine era were from developed European and North American countries, whereas most studies in the vaccine era were from least developed or developing countries in Asia and Africa. When vaccine era R_0 estimates were stratified by UN development status, the vaccine-era median measles R_0 was higher in the least developed or developing countries compared with developed countries. Thus, the high R_0 in the vaccine era might reflect skewing of the median R_0 due to a high proportion of studies from least developed or developing country settings, where birth rate, population density, and measles burden all tend to be higher. Our finding could also be explained by poor data quality in either study setting. Findings from stratification of R_0 by birth rate or population density were more intuitive. High birth rate or high population density were associated with high R_0. In fact, the outcomes of one study showed a positive relationship between population density and R_0 for India and for included African countries.[20] In the case of birth rate and population density, our stratifications divided roughly into European and North American versus Indian and African estimates. Whether birth rate and population density are key determinants of measles R_0 that vary by region and country development status merits further study. Population size, independent of density and birth rate, might be another consideration.[33] Additional covariates that are likely to vary with region and degree of development include contact patterns as dictated by social determinants including cultural practices, nutrition, climate and seasonality, infection control measures including social distancing and quarantine, and, in post-elimination settings, the effect of waning immunity and importations. Median measles R_0 also varied with the type of data used to generate the estimate. Differences in R_0 by data source could be affected by the quality of surveillance data, which would be of particular concern in resource poor settings.[20,34] Several of the reviewed studies included serological survey data, which has well known limitations, in particular, sampling bias (eg, healthy worker or sick populations, which could overestimate or underestimate population immunity, and thereby overestimate or underestimate R_0), but these were unlikely sources of bias in the reviewed studies.

R0 in the literature

Variations in R_0 estimates are not unique to measles. Although dengue virus is vector borne and therefore has different transmission dynamics than measles, a broad range of R_0 estimates have been reported for dengue, ranging from 0·5 to 103 on the basis of 12 publications, and study authors acknowledge that some of those differences might be attributable to different methods of R_0 estimation,[32] an issue that is underscored in another summary of 2009 H1N1 R_0 values.[31] If R_0 is to be used to inform public health officers when setting vaccine coverage targets, then standardised methods of calculation and reporting are required; however, despite the dramatic increase in the number of publications with R_0 estimates since 2000,[30] standardised methods have not been established. A plethora of R_0 calculation methods exist in the statistical and mathematical modelling literature,[35–38] and the resulting R_0 values vary depending on the method and model assumptions. On the basis of the different R_0 values reported in this systematic review for the same outbreaks but by different authors using different methods,[20,21,24] it may be prudent to apply multiple estimation methods to the same data and compare the resulting R_0 values until a gold standard method is established. Methods for R_0 calculations are not without limitations.[30,35–37,39] For example, using case-count time-series data can result in an R_0 estimate that best represents the population presenting most cases and might be a poor estimate if extrapolated to other populations.[40] Furthermore, using different age-specific contact pattern matrices can yield substantially different R_0 estimates.[18] A best move forward in determining R_0 across different outbreaks might therefore be to always employ one or two very simple methods. Furthermore, it would be prudent to extend epidemic or outbreak studies to include one or two more complex methods that can consider age-related data, temporal data, or contact network structure so comparisons across methods can be made. As a result, R_0 values of the same pathogen can be compared across epidemics, and a range of R_0 will be determined for one

outbreak. The resulting ranges can then be used to inform vaccination coverage targets, data acquisition, and best modelling practices.

The variable quality and application of R_0 calculations has been recognised globally. As a result, WHO has appointed modellers onto advisory committees to quantify and critique this variability (ie, the Immunization and Vaccines-Related Implementation Research Advisory Committee [IVIR-AC]).[41] Moving forward, these recommendations, and the quality assurance guidelines provided by GRADE,[42] should be considered in all modelling studies and R_0 calculations of measles outbreaks so that public health decision making is best informed.

At the study level, data quality was a potential weakness in all studies reviewed (table 1), in particular those using multiple secondary sources of data. The measles R_0 synthesis across studies should be interpreted with the following limitations in mind. We restricted our search to articles written in English because of resource limitations, and this might have excluded relevant, high-quality studies and might have resulted in a selection of published articles weighted towards English language speaking countries. We also limited our systematic review to published literature held in MEDLINE, Embase, and Global Health databases, which are unlikely to capture many governmental or agency reports unless they are published in an indexed journal. The sensitive search strategy, however, produced a comprehensive search of these databases. For stratification by WHO region, only one published article and one country were included in the southeast Asia region. If method of estimation can affect R_0 values, then the estimates presented for southeast Asia might be skewed or might not be balanced by a diversity of estimation methods as was the case for Europe and, to a lesser extent, Africa. Population density seemed like an obvious covariate given the centrality of contact for measles transmission; however, country-level density data do not always reflect how density ranges from rural to urban communities within the same country. Additionally, reliability of R_0 across studies could be affected by the types, specificity, and sensitivity of diagnostic assays and algorithms used to measure burden or susceptibility. To our knowledge, no validated quality assessment tool exists for conduct or reporting of modelling studies, although some best-practice standards exist.[43,44] The limited number of systematic reviews on R_0 meant that there were limited validated approaches for synthesising measures of R_0. Given the growth in infectious disease dynamics data being generated by models,[35,45] reporting and quality appraisal guidelines are needed. Finally, methods of R_0 calculation varied amongst the studies.

Measles R_0 estimates are highly relevant to measles elimination efforts and can be used to estimate the level of vaccination coverage needed to prevent endemic transmission. Our results highlight the importance of country-specific R_0 estimates based on national estimates given the variation in reported measles R_0 values. In some cases, country-level data might not be ideal if settings within the country vary widely in terms of R_0 covariates, although resources and data quality can limit the extent to which extension to sub-national level is appropriate. In that situation, a two-stage process might be to follow up regular national-level R_0 calculations with targeted calculations in locations or groups suspected to have immunity gaps. To calculate local R_0 estimates for accurate vaccination coverage targets, countries need high-quality surveillance data and high-quality census data to either provide denominator values or, if R_0 estimates are to be extrapolated from a similar setting, inform which settings are most similar in terms of key R_0

	Range	Median (number of publications, number of estimates)
Data sources		
Surveillance*[10,13,15,16,19,21,24,26]	4·6–44·4	13·2 (8, 12)
Seroprevalence, with or without surveillance[12,17,18,23]	3·7–203·3	16·1 (5, 24)
Outbreak[11,22,25,27]	6·2–32·1	9·9 (4, 8)
Measles vaccine era		
Pre-vaccine programme[7,10–13,15–17]	6·1–27·0	11·1 (8, 14)
Vaccine programme[7,20–27]	3·7–203·3	15·7 (9, 29)
UN development status		
Developed[7,12,13,15–19,22,23,25,26]	6·1–45·4	12·9 (13, 24)
Pre-vaccine era[7,12,13,15,17]	6·1–18·0	12·5 (5, 9)
Vaccine era[7,22,23,25–27]	6·2–32·1	11·7 (6, 10)
Least developed†	..	..
Vaccine era[20,21,24]	3·7–203·3	15·9 (3, 19)
WHO region		
Americas[7,16,26]	10·7–27·0	15·3 (3, 4)
Europe[7,12,13,15,17–19,22,23,25,27]	6·1–45·4	12·9 (11, 20)
Africa[20,21,24]	4·6–203·3	12·8 (3, 11)
South-east Asia[20]	3·7–26·3	16·4 (1, 8)
Population density (post-1900)		
<1000 people per km² [7,12,16,17,19–23,26]	3·7–203·3	12·6 (10, 20)
Americas[7,16,26]	10·7–27·0	15·3 (3, 4)
Europe[7,12,17,19,22,23]	6·1–34·7	11·5 (6, 10)
Africa[20,21]	4·6–203·3	12·8 (2, 5)
Southeast Asia[20]	3·7–21·4	6·7 (1, 4)
≥1000 people per km² [13,15,19,20,24,27]	4·7–68·8	15·9 (6, 19)
Americas	..	..
Europe[13,15,19,25,27]	6·2–57·0	12·4 (4, 6)
Africa[20,24]	4·7–68·8	15·7 (2, 7)
Southeast Asia[20]	10·0–26·3	16·4 (1, 6)
Birth rate		
≤20 births per 1000 people[16,17,19,22,23,25,26,27]	6·1–34·7	10·4 (8, 14)
>20 births per 1000 people[10–12,20,21,24]	3·7–203·3	12·9 (6, 24)

R_0=basic reproduction number. *Includes one school entry survey. †Least developed countries by UN classification criteria,[9] plus Kenya, India, Cameroon.

***Table 2*: Measles R_0 range and median by covariate**

For **IVIR-AC** see http://www.who.int/immunization/research/committees/ivir_ac/en/

covariates.[17] In the absence of comprehensive, setting-specific R_0 estimates, mathematical modelling of R_0 can offer primary or complementary evidence to study measles transmission dynamics;[35,43,45] however, parameterising models with setting-specific data or data from similar contexts is crucial. When global and regional coverage targets are reviewed, they might need adapting at country level to take account of the local context and the most locally appropriate estimate of R_0 on which to base coverage targets. The observation that about half of the R_0 estimates from our systematic review were less than the 12–18 range supports the argument that accurate R_0 values are necessary because small differences in R_0 at the low end of the range can give very different estimates of coverage required for achieving elimination. We certainly would not, however, wish the variation in R_0 estimates to be interpreted as indicating that measles coverage targets should be relaxed. Observations from the field indicate inconsistencies in occurrence of outbreaks and reported coverage, but it is difficult to separate out the effects of variation in coverage data quality, age-specific vaccine effectiveness, and potential local variation in R_0, all of which contribute to the population herd immunity threshold. One constant is that coverage always needs to be higher than the herd immunity threshold to adjust for vaccine effectiveness. In addition to high-quality coverage monitoring, surveillance, and census data, countries would need the knowledge base, tools, and expert support to generate R_0 estimates. Resources to estimate reproduction numbers have emerged in recent years,[44,46,47] but one could argue that consideration of R_0 during elimination efforts is undervalued. In addition to informing levels of vaccination required for elimination, R_0 can be used in evaluating the effectiveness of an intervention to alter disease dynamics or to anticipate the size and duration of an outbreak, thereby informing public health preparedness and action.[48] WHO recommendations on lines of evidence to verify measles elimination are somewhat flexible to accommodate differing existing surveillance systems.[49] These recommendations could include R_0 to inform elimination efforts and as a form of evidence of changing transmission dynamics.[50] Given the variability of R_0 values generated using different methods of calculation, one of the most reasonable applications of R_0 could be using the same methods to monitor a population's progress towards or maintenance of elimination. Alternatively, the related effective reproduction number might be a more intuitive measure than the basic reproduction number, and similar to R_0, approaches to calculating R_e exist. For example, in countries having achieved measles elimination but without a completely immune population, an estimate of potential transmission from imported cases would be of interest.[51] If R_e is less than 1, not every case will result in a new infection in another individual, and transmission will cease even if there are small chains of transmission.

Conclusion

R_0 describes transmissibility within a population and is highly dependent on that population and the method of calculation. We present evidence that depending on the context, measles R_0 may be different than the frequently cited range of 12–18. Context-specific estimates of R_0 are needed to determine the feasibility of achieving local measles elimination.

Declaration of interests

JH has collaborated with vaccine companies Medicago and Sanofi Pasteur, but these collaborations were outside the current work. The remaining authors declare no competing interest. The opinions, results, and conclusions reported in this paper are those of the authors and are independent from the funding sources.

Contributors

NSC, GL, and FMG designed the study. FMG and GL screened the literature for relevancy. FMG and SB did the data extraction and quality appraisal. JH, NSC, SB, and SLD resolved any disagreements in study relevancy, extraction, and quality appraisal. FMG, GL, and YL did the data analysis. FMG drafted and revised the manuscript. All authors participated in data interpretation and revised the manuscript for intellectual content.

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References

1 Bentley J, Rouse J, Pinfield J. Measles: pathology, management and public health issues. *Nurs Stand* 2014; **28:** 51–58.
2 Hajj Hussein I, Chams N, Chams S, et al. Vaccines through centuries: major cornerstones of global health. *Front Public Health* 2015; **3:** 269.
3 Cutts FT, Lessler J, Metcalf CJ. Measles elimination: progress, challenges and implications for rubella control. *Expert Rev Vaccines* 2013; **12:** 917–32.
4 WHO. Proceedings of the Global Technical Consultation to assess the feasibility of measles eradication, 28–30 July 2010. *J Infect Dis* 2011; **204** (suppl 1): S4–13.
5 Anderson R, May R. Infectious disease of humans. Oxford: Oxford University Press, 1991: 768.
6 Vynnycky E, White R. An introduction to infectious disease modelling. Oxford: Oxford University Press, 2010.
7 Anderson RM, May RM. Directly transmitted infections diseases: control by vaccination. *Science* 1982; **215:** 1053–60.
8 Anderson RM, May RM. Age-related changes in the rate of disease transmission: implications for the design of vaccination programmes. *J Hyg (Lond)* 1985; **94:** 365–436.
9 Rosella L, Bowman C, Pach B, Morgan S, Fitzpatrick T, Goel V. The development and validation of a meta-tool for quality appraisal of public health evidence: Meta Quality Appraisal Tool (MetaQAT). *Public Health* 2016; **136:** 57–65.
10 Paterson BJ, Kirk MD, Cameron AS, D'Este C, Durrheim DN. Historical data and modern methods reveal insights in measles epidemiology: a retrospective closed cohort study. *BMJ Open* 2013; **3:** e002033.
11 Becker NG, Hasofer AM. Estimating the transmission rate for a highly infectious disease. *Biometrics* 1998; **54:** 730–38.
12 Merler S, Ajelli M. Deciphering the relative weights of demographic transition and vaccination in the decrease of measles incidence in Italy. *Proc Biol Sci* 2014; **281:** 20132676.
13 Metcalf CJ, Bjornstad ON, Grenfell BT, Andreasen V. Seasonality and comparative dynamics of six childhood infections in pre-vaccination Copenhagen. *Proc Biol Sci* 2009; **276:** 4111–18.
14 Dietz K. Transmission and control of arboviruses. In: Ludwig D, Cooke KL, eds. Proceedings of the SIMS conference on epidemiology. Philadelphia, PA: Society for Industrial and Applied Mathematics, 1975: 104–21.

15 Olsen LF, Truty GL, Schaffer WM. Oscillations and chaos in epidemics: a nonlinear dynamic study of six childhood diseases in Copenhagen, Denmark. *Theor Popul Biol* 1988; **33:** 344–70.

16 Hooker G, Ellner SP, Roditi Lde V, Earn DJ. Parameterizing state-space models for infectious disease dynamics by generalized profiling: measles in Ontario. *J R Soc Interface* 2011; **8:** 961–74.

17 Edmunds WJ, Gay NJ, Kretzschmar M, Pebody RG, Wachmann H, ESEN Project. European Sero-epidemiology Network. The pre-vaccination epidemiology of measles, mumps and rubella in Europe: implications for modelling studies. *Epidemiol Infect* 2000; **125:** 635–50.

18 Wallinga J, Levy-Bruhl D, Gay NJ, Wachmann CH. Estimation of measles reproduction ratios and prospects for elimination of measles by vaccination in some western European countries. *Epidemiol Infect* 2001; **127:** 281–95.

19 He D, Ionides EL, King AA. Plug-and-play inference for disease dynamics: measles in large and small populations as a case study. *J R Soc Interface* 2010; **7:** 271–83.

20 Szusz EK, Garrison LP, Bauch CT. A review of data needed to parameterize a dynamic model of measles in developing countries. *BMC Res Notes* 2010; **3**: 75-0500-3-75.

21 Broutin H, Mantilla-Beniers NB, Simondon F, et al. Epidemiological impact of vaccination on the dynamics of two childhood diseases in rural Senegal. *Microbes Infect* 2005; **7:** 593–99.

22 Mossong J, Muller CP. Estimation of the basic reproduction number of measles during an outbreak in a partially vaccinated population. *Epidemiol Infect* 2000; **124:** 273–78.

23 Wallinga J, Teunis P, Kretzschmar M. Reconstruction of measles dynamics in a vaccinated population. *Vaccine* 2003; **21:** 2643–50.

24 Grais RF, Ferrari MJ, Dubray C, et al. Estimating transmission intensity for a measles epidemic in Niamey, Niger: lessons for intervention. *Trans R Soc Trop Med Hyg* 2006; **100:** 867–73.

25 van Boven M, Kretzschmar M, Wallinga J, O'Neill PD, Wichmann O, Hahne S. Estimation of measles vaccine efficacy and critical vaccination coverage in a highly vaccinated population. *J R Soc Interface* 2010; **7:** 1537–44.

26 Glasser JW, Feng Z, Omer SB, Smith PJ, Rodewald LE. The effect of heterogeneity in uptake of the measles, mumps, and rubella vaccine on the potential for outbreaks of measles: a modelling study. *Lancet Infect Dis* 2016; **16:** 599–605.

27 Plans Rubio P. Is the basic reproductive number (R_0) for measles viruses observed in recent outbreaks lower than in the pre-vaccination era? *Euro Surveill* 2012; **17:** 22.

28 Vivancos R, Keenan A, Farmer S, et al. An ongoing large outbreak of measles in Merseyside, England, January to June 2012. *Euro Surveill* 2012; **17:** 20226.

29 Department of Economic and Social Affairs of the United Nations Secretariat (DESA). 2015 country snapshots. 2015. http://www.un.org/en/development/desa/policy/cdp/cdp_publications/2015_ldc_factsheet_all.pdf (accessed June 25, 2017).

30 Ridenhour B, Kowalik JM, Shay DK. Unraveling R_0: considerations for public health applications. *Rev Panam Salud Publica* 2015; **38:** 167–76.

31 Biggerstaff M, Cauchemez S, Reed C, Gambhir M, Finelli L. Estimates of the reproduction number for seasonal, pandemic, and zoonotic influenza: a systematic review of the literature. *BMC Infect Dis* 2014; **14:** 1471-2334-14-480.

32 Johansson MA, Hombach J, Cummings DA. Models of the impact of dengue vaccines: a review of current research and potential approaches. *Vaccine* 2011; **29:** 5860–68.

33 Yoshikura H. Impact of population size on incidence of rubella and measles in comparison with that of other infectious diseases. *Jpn J Infect Dis* 2015; **68:** 80.

34 McLean AR, Anderson RM. Measles in developing countries. Part I. Epidemiological parameters and patterns. *Epidemiol Infect* 1988; **100:** 111–33.

35 Breban R, Vardavas R, Blower S. Theory versus data: how to calculate R_0? *PLoS One* 2007; **2:** e282.

36 Heffernan JM, Smith RJ, Wahl LM. Perspectives on the basic reproductive ratio. *J R Soc Interface* 2005; **2:** 281–93.

37 Li J, Blakeley D, Smith RJ. The failure of R_0. *Comput Math Methods Med* 2011; **2011:** 527610.

38 Thompson KM. Evolution and use of dynamic transmission models for measles and rubella risk and policy analysis. *Risk Anal* 2016; **36:** 1383–403.

39 Holme P, Masuda N. The basic reproduction number as a predictor for epidemic outbreaks in temporal networks. *PLoS One* 2015; **10:** e0120567.

40 Cori A, Ferguson NM, Fraser C, Cauchemez S. A new framework and software to estimate time-varying reproduction numbers during epidemics. *Am J Epidemiol* 2013; **178:** 1505–12.

41 Stevens GA, Alkema L, Black RE, et al. Guidelines for accurate and transparent health estimates reporting: the GATHER statement. *Lancet* 2016; **388:** e19–e23.

42 Guyatt GH, Oxman AD, Schunemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the *Journal of Clinical Epidemiology*. *J Clin Epidemiol* 2011; **64:** 380–82.

43 Pitman R, Fisman D, Zaric GS, et al. Dynamic transmission modeling: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force Working Group-5. *Med Decis Making* 2012; **32:** 712–21.

44 Obadia T, Haneef R, Boelle PY. The R0 package: a toolbox to estimate reproduction numbers for epidemic outbreaks. *BMC Med Inform Decis Mak* 2012; **12:** 1472-6947-12-147.

45 Heesterbeek H, Anderson RM, Andreasen V, et al. Modeling infectious disease dynamics in the complex landscape of global health. *Science* 2015; **347:** aaa4339.

46 Hyman JM, Li J. An intuitive formulation for the reproductive number for the spread of diseases in heterogeneous populations. *Math Biosci* 2000; **167:** 65–86.

47 Fisman DN, Hauck TS, Tuite AR, Greer AL. An IDEA for short term outbreak projection: nearcasting using the basic reproduction number. *PLoS One* 2013; **8:** e83622.

48 Louz D, Bergmans HE, Loos BP, Hoeben RC. Emergence of viral diseases: mathematical modeling as a tool for infection control, policy and decision making. *Crit Rev Microbiol* 2010; **36:** 195–211.

49 Framework for verifying elimination of measles and rubella. *Wkly Epidemiol Rec* 2013; **88:** 89–99.

50 Gidding HF, Martin NV, Stambos V, et al. Verification of measles elimination in Australia: Application of World Health Organization regional guidelines. *J Epidemiol Glob Health* 2016; **6:** 197–209.

51 De Serres G, Gay NJ, Farrington CP. Epidemiology of transmissible diseases after elimination. *Am J Epidemiol* 2000; **151:** 1039–52.