Measles Outbreak Investigation Process in Low- and Middle-Income Countries: A Systematic Review of the Methods and Costs of Contact Tracing

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Abstract

Aim: The occurrence of measles outbreaks has increased, and previously measles-free countries are experiencing a resurgence, making measles elimination by 2020 unlikely. Therefore, outbreak prevention and rapid response strategies will need to be intensified. This systematic review therefore examines whether Contact Tracing (CT) as compared to no CT is an effective means of reducing measles spread during outbreaks in Low- and Middle-Income Countries (LMICs).

Subject and Methods: A systematic review was conducted by searching 6 databases (CINAHL, Global Health, Medline, Cochrane Library, Web of Science, and PubMed). The 17 included articles were appraised using the Critical Appraisal Skills Programme checklists and analysed using a narrative synthesis.

Results: CT is often used alongside mass communication strategies and hospital record checks. Interviewing measles cases to identify contacts, and considering everyone who has shared a space with a case as a contact are common CT methods. Also, CT can be done backwards and/or forwards with the measles case as the focal point of the investigation process. The cost per case of an outbreak response dominated by CT is high especially in terms of labour for the health sector and productivity losses for households. However, overall outbreak expenditure can be low if CT results in fewer and less severe measles cases and a short outbreak duration.

Conclusion: CT data as a standalone and comparative active surveillance approach in LMICs is scarce. If CT is initiated early, it can prevent large outbreaks thereby reducing the economic burden of measles and drive LMICs towards measles elimination.

Keywords*: Measles outbreak, Contact tracing, Economic costs, Low- and middle-income countries*

Introduction

Measles is a highly infectious airborne, acute and vaccine-preventable disease of viral origin (Moss 2017). Prior to vaccine use and the revival of immunisation programmes, measles accounted for high child morbidity and mortality (Moss 2017) with at least 95% of children aged under 15 years having had measles (WHO [World Health Organisation] 2017), resulting in over 2

million deaths and 15,000 to 60,000 cases of blindness worldwide per annum. Safe and cost-effective combination (measles, rubella and mumps) vaccines have reduced global measles deaths to 535,000 in 2000 and 139,000 in 2010 (WHO 2012).

The WHO set 2020 as the target for measles elimination in at least five of its regions and at the core of this global strategic plan for measles/rubella control and elimination, is outbreak preparedness and responsiveness (WHO 2012). As an essential component of measles outbreak investigation and response (Ghebrehewet et al. 2016), Contact Tracing (CT) identifies, tracks and follow-up individuals who have had direct contact with an infected individual (WHO 2015) to identify who infected the case and who the case may have infected (Sniadack, Crowcroft, Durrheim and Rota 2017).

Numerous cases of measles go unreported (Strebel et al. 2011) and globally, about 20 million individuals are susceptible to measles and rubella (Measles and Rubella Initiative 2018) while persistent endemicity of measles in some countries fosters importation and thus outbreaks in other countries (WHO 2018). Though developed countries are not the main focus of this paper, such importations and poor vaccine coverage have been implicated in the re-emergence of measles in Europe and the United States of America (USA) over the past decade (Abad and Safdar 2015; Siani 2019). In addition, outbreaks of measles are on the rise and there are indications that measles cases increased by 300% in the first quarter of 2019 with outbreaks occurring in eleven Low- and Middle-income Countries (LMICs) relative to the same period in 2018 (WHO 2019).

Consequently, eliminating measles by the year 2020 (WHO 2012) has been considered an unrealistic ambition given that none of the six WHO regions had achieved an earlier 2015 milestone of 95% coverage in supplementary vaccination in every health district (Dabbagh et al. 2018; Orenstein, Hinman, Nkowane, Olive and Reingold 2018). Furthermore, there are indications that the core elements of the global strategic plan for measles are executed partially or are not tailored to local needs (Orenstein et al. 2018), and thirteen countries are significantly off-track for measles elimination in the WHO African Region (WHO Regional Committee for Africa 2017).

CT is resource-intensive and its use in outbreaks may be limited by the competition for scarce resources with other outbreak response activities. Delaying to initiate CT because of limited resources makes a later attempt to trace contacts more expensive as exposures would have increased exponentially (WHO 2015). LMICs experience the highest measles incidence and mortality with very few certified as measles-free in 2017 (Dabbagh et al. 2018), yet, the share of healthcare in their government budgets remains low with an overreliance on donors and the private sector (Piatti-Fünfkirchen, Lindelow and Yoo 2018). Also, donor fatigue and reduced interest of countries in issues perceived as mainly associated with developing countries have been identified (Hinman 2018). This represents a potential challenge in obtaining financial support for measles outbreak response. Therefore, gaining insights into the economic costs of CT is essential as it will build a case for a full economic evaluation and inform investment in preventive strategies to sustain measles eradication efforts as well as those of other infectious diseases. The aim of this systematic review is to investigate whether CT as compared to no CT is an effective means of reducing the spread of measles during outbreaks in LMICs by determining methods used in CT and the economic costs of CT during measles outbreaks.

Methods

This study used a systematic review approach as outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher, Liberati, Tetzlaff, Altman, and Group 2009), whose completed checklist can be found in Online Resource 1. The inclusion criteria for this study were as follows: journal articles published in English, within the past 30 years, of any study design and that reported measles as an outbreak; use of CT in measles outbreak investigations; and measles outbreaks within the community and/or hospital. The exclusion criteria were: journal articles reporting rubella only or isolated measles cases (where no outbreak was declared), or measles outbreaks in developed countries even if reported to have been imported from a LMIC; and studies published in a language other than English, or for which the full text was not available.

Search Strategy and Study Selection

Six electronic databases (CINAHL, Global Health, Medline, Cochrane Library, Web of Science and PubMed Central Open Access) were searched in July 2019. The selection of search terms was guided by the PICO (Population, Intervention, Comparator, Outcome) format as shown in Table 1 below and the use of closely related words from background/existing literature. These terms were applied individually then combined using two Boolean operators "OR" and "AND" as outlined in Table 2 below. Other relevant articles were identified by hand searching the reference lists of included articles. Two main reviewers (ELM and ML) decided on the search terms to be used and the data to be extracted. Any disagreements regarding literature inclusion, data extraction or quality assessment were reviewed and settled by the third reviewer (JCH).

Table 1 Keywords used in database searches

Table 2 Article Search Strategy

Quality Appraisal

The various CASP (Critical Appraisal Skills Programme) checklists were used to appraise the quality of evidence in the selected articles (CASP 2018). The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist (von Elm et al. 2007) was applied to critically appraise selected articles that had a cross-sectional design since a checklist dedicated to cross-sectional studies was not available within the CASP at the time of this review.

Data Extraction

A form for data extraction was created on Excel, piloted and refined to improve its validity. ELM and ML independently reviewed the included studies for data on article features (author, title, country of origin, and design), participant demographics, methods, results, limitations and funding. The Mendeley referencing software was used to track all references and selected full-text articles.

Data Analysis and Synthesis

An overview of the included studies was first given using a descriptive synthesis. This was followed by a thematic analysis to evaluate the exhaustiveness of evidence within the included articles and to determine the relationships that exist within and between them (Centre for Reviews and Dissemination University of York 2009). A narrative synthesis of the findings of included studies was conducted together with an explanation of how and for whom CT works. Also, the relationship between and within these articles was explored by concept mapping and a visual illustration of the relationship between study features/results. Lastly, a critical reflection on the synthesis process was conducted to identify its strengths and weaknesses and to inform the review's conclusions and recommendations.

Study Registration

This systematic review was internally registered with the Academic Ethics Committee for Bangor University and was granted exemption from requiring ethics approval (as study did not involve human participants), and externally with PROSPERO (an international Prospective Register of Systematic Reviews), registration number CRD42019142794.

Results

The Article Selection Process

Database searches identified 617 studies and the details of this process has been presented in Table 2 above. After screening study titles and abstracts, 371 and 113 articles were excluded respectively because the research was not conducted in a LMIC, or the area of focus was not measles or measles outbreak, or there was no CT or outbreak investigation. The full-texts of 133 articles were read for eligibility and 109 articles were excluded because the articles did not have content on CT or the full-text was not in English. Across all databases, 11 duplicates were removed leaving 13 articles whose reference lists were hand-searched revealing 4 additional articles and resulting in a total of 17 articles included in this review. Figure 1 below is a modified PRISMA flow diagram (Moher et al. 2009) showing how the study selection was conducted. A summary of the article selection process can be found in Online Resource 2. Also see Online Resource 3 for the study selection process of each database.

Fig. 1 Article Selection Process

Characteristics of Selected Studies

The following subsections have incorporated the PICO framework (though the comparator [C] is absent as studies comparing CT to no CT were not found) into the description of the main study characteristics and more information can be found in Table 3 and Table 4 below.

Table 3 Main Characteristics of Studies on Contact Tracing (CT) Methods

Table 4 Main Characteristics of Contact Tracing (CT) Cost Analysis Studies

Study Population

From the 17 studies included in this review, 4 articles were from China (Jin et al. 2011; Ma et al. 2016; Ma et al. 2017; Zhang et al. 2015), 3 from Senegal (Cisse et al. 1999; Garenne and Aaby 1990; Whittle et al. 1999), 2 from the Federated States of Micronesia (Hales et al. 2016; Pike et al. 2017), and 1 each from India (Rathi et al. 2017), Bolivia (Quiroga et al. 2003), Brazil (Lemos et al. 2017), Venezuela (Sarmiento et al. 2011), Republic of Marshall Islands (Marin et al. 2006), Romania (Njau et al. 2019), Tanzania(Goodson et al. 2010), and Ethiopia (Wallace et al. 2014). Eleven of the studies involved both male and female participants and the remaining 6 had no data on sex distribution of subjects (Garenne and Aaby 1990; Marin et al. 2006; Pike et al. 2017; Quiroga et al. 2003; Sarmiento et al. 2011; Wallace et al. 2014). Most (88.2%) of the studies included both children and adults, but two studies included children (Whittle et al. 1999) and young adults (Jin et al. 2011) only. With regards to population density, three studies reported high numbers of persons per household (Garenne and Aaby 1990; Hales et al. 2016; Marin et al. 2006). Several studies highlighted crowding at public events like football competitions (Lemos et al. 2017), university environments (Jin et al. 2011; Rathi et al. 2017), hospital units (Zhang et al. 2015), large cities (Goodson et al. 2010; Quiroga et al. 2003) and work environments (Ma et al. 2017).

Interventions

To trace contacts, cases were located through surveillance records and contacts solicited through case or caregiver/parent interview (Garenne and Aaby 1990; Goodson et al. 2010; Hales et al. 2016; Ma et al. 2016; Whittle et al. 1999). In other studies (Jin et al. 2011; Ma et al. 2017; Marin et al. 2006; Quiroga et al. 2003; Rathi et al. 2017; Zhang et al. 2015), the contacts were approached directly after locating the places where the cases worked or lived. One study established a contact list and followed-up everyone sharing a home or enclosed space with the case (Sarmiento et al. 2011), another obtained a list of exposed pupils from the school register (Cisse et al. 1999), and a third used the picture of a measles case to search for contacts within the community (Lemos et al. 2017). CT was implemented alongside mass communication strategies (Lemos et al. 2017; Ma et al. 2017; Rathi et al. 2017), and vaccinators to search for cases (Quiroga et al. 2003).

All the cost analysis studies adopted a societal perspective, used the United States Dollars (USD) as the unit of measuring costs, and collected data on both direct and indirect costs of the outbreak and response. One study costed CT among other outbreak response activities (Pike et al. 2017) and contact vaccination was part of the outbreak response cost items in another study (Njau et al. 2019). In an Ethiopian study (Wallace et al. 2014), active surveillance was part of the health sector costs, and a Chinese study estimated the proportion of personnel time used in CT as part of outbreak response activities (Ma et al. 2017).

Outcomes

Contact Tracing and Prevention of Measles Spread

In this systematic review, prevention of measles spread was assessed by length of outbreak and magnitude/size of outbreak (number of cases and deaths) which is similar to the case-day index, a measure validated by comparing contacts per case and contacts per day ratios (Ortega-Sanchez, Vijayaraghavan, Barskey and Wallace 2014).

The length of the measles outbreak in the included studies varied from 19 days (Ma et al. 2017) to over 30 months (Quiroga et al. 2003). Six of the studies had outbreaks lasting for 6 months or less (Hales et al. 2016; Jin et al. 2011; Ma et al. 2016; Marin et al. 2006; Rathi et al. 2017; Zhang et al. 2015). One study's outbreak duration was 8 months (Goodson et al. 2010), two other studies had outbreaks for 9 months (Cisse et al. 1999; Whittle et al. 1999), another for 12 months (Sarmiento et al. 2011), and one other for as long as 20 months (Lemos et al. 2017). One study (Garenne and Aaby 1990) had an unclear outbreak length as the study seems to have involved several outbreaks over a 4-year-period.

The number of cases identified in some studies were 1500 cases (Garenne and Aaby 1990), 280 cases (Ma et al. 2016), 122 cases (Sarmiento et al. 2011), 2567 cases (Quiroga et al. 2003), 45 cases (Zhang et al. 2015), and 209 cases (Cisse et al. 1999). No deaths were recorded by some studies (Ma et al. 2017; Rathi et al. 2017; Sarmiento et al. 2011; Whittle et al. 1999). A small proportion of studies reported few deaths: 4 deaths (Quiroga et al. 2003), 1 stillbirth (Cisse et al. 1999), 1 death (Hales et al. 2016) and a case fatality ratio of 6.5% (Garenne and Aaby 1990).

Economic Costs of Contact Tracing

It is recognised that there is an economic cost associated with CT. Containment cost (contact tracing inclusive), productivity losses, and direct medical and non-medical cost accounted for 90%, 6% and 4% of the outbreak expenditure respectively (Pike et al. 2017). Research findings indicate that 17% of total outbreak cost was spent on contact and high-risk group vaccines (Njau et al. 2019). The economic cost of active surveillance was estimated at $117,302 ($22.31/case) compared to $380,052 ($72.29/case) for outbreak response immunisation (Wallace et al. 2014) with 77.5% of personnel time spent on CT alone (Ma et al. 2017).

Quality and Risk of Bias Assessment

Two secondary attack rate studies (Hales et al. 2016; Marin et al. 2006) and four studies whose design was not explicitly stated (Cisse et al. 1999; Garenne and Aaby 1990; Rathi et al. 2017; Whittle et al. 1999) were classified as cohort studies based on the reviewer's evaluation and the corresponding CASP tool (CASP 2018) was used to appraise their quality (See table 1, Online Resource 4). All the studies had clearly stated objectives, the method of recruiting cohorts was acceptable and the findings were in line with existing evidence with huge practice implications. Three of the included studies used a case-control design (Goodson et al. 2010; Jin et al. 2011; Zhang et al. 2015) and were assessed for quality using the CASP case-control tool (CASP 2018). In these three studies, all cases and controls were randomly selected and treated equally,

confounding was minimised, the treatment effects were large, and each study's findings were in line with existing evidence (See table 2, Online Resource 4).

One of the included studies was clearly identified as descriptive (Lemos et al. 2017) and three others whose design was not clearly stated (Ma et al. 2016; Quiroga et al. 2003; Sarmiento et al. 2011) were added to this category because there was no investigation of causal relationships (Aggarwal and Ranganathan 2019) and assessed using the STROBE checklist (von Elm et al. 2007). These studies were scientifically acceptable; clearly and elaborately described measles outbreaks plus response activities (See table 3, Online Resource 4).

Four of the studies (Ma et al. 2017; Njau et al. 2019; Pike et al. 2017; Wallace et al. 2014) were partial economic evaluations. To assess their quality, the CASP tool for full economic evaluations was adapted by excluding its comparator and marginal analysis items and including items common to CHEERS, Consolidated Health Economic Evaluation Reporting Standards (Husereau et al. 2013) and QHES, Quality of Health Economic Studies (Ofman et al. 2003) tools whose assessment findings have been shown to be comparable (Monten, Veldeman, Verhaeghe, and Lievens 2017). All four studies had clear objectives; discussed how costs were identified, valued and measured; and clearly stated the perspective of economic evaluation (See table 4, Online Resource 4).

For risk of bias assessment, non-random sampling methods such as convenience sampling (Hales et al. 2016; Lemos et al. 2017; Marin et al. 2006; Zhang et al. 2015) or purposive sampling (Ma et al. 2016; Rathi et al. 2017) and non-response bias (Goodson et al. 2010; Ma et al. 2016; Wallace et al. 2014; Whittle et al. 1999) were the main reasons for selection bias. For information bias ratings, most of the studies were found to have recall bias (Cisse et al. 1999; Garenne and Aaby 1990; Goodson et al. 2010; Jin et al. 2011; Marin et al. 2006; Rathi et al. 2017; Sarmiento et al. 2011; Wallace et al. 2014; Zhang et al. 2015) and a few others detection bias (Garenne and Aaby 1990; Lemos et al. 2017; Marin et al. 2006; Sarmiento et al. 2011). For confounding, the reasons were variable across studies and details can be found in Online Resource 5.

Thematic Analysis and Narrative Synthesis

Methods of Contact Tracing

CT can be done by case/caregiver referral where cases are located through surveillance records and contacts are solicited by interviewing the case or caregiver/parent (Garenne and Aaby 1990; Goodson et al. 2010; Hales et al. 2016; Ma et al. 2016; Whittle et al. 1999). CT can also be conducted by shared space identification with contacts approached directly after locating the places where the cases work or live through routinely reported data (Jin et al. 2011; Ma et al. 2017; Marin et al. 2006; Quiroga et al. 2003; Rathi et al. 2017; Zhang et al. 2015) or by establishing a contact list and following up everyone sharing a home or enclosed space with the case (Sarmiento et al. 2011).

School registers can also be used as a method of CT by obtaining a list of exposed pupils and mapping out classroom sitting positions with the help of teachers (Cisse et al. 1999). Other school-

related outbreaks utilise teachers for daily rash and temperature/fever checks (Jin et al. 2011) or interview staff working at student residential halls to report new cases (Rathi et al. 2017). The picture of a measles case can also be used to search for contacts within the community (Lemos et al. 2017).

CT is part of an integrated active surveillance approach. Therefore, it is often combined with other strategies such as mass communication strategies (Lemos et al. 2017; Ma et al. 2017; Rathi et al. 2017), hospital record checks (Lemos et al. 2017; Sarmiento et al. 2011; Zhang et al. 2015) or having vaccinators search for cases as they move from house to house (Quiroga et al. 2003).

Forward versus Backward Contact Tracing

With the index case as the focal point, CT can be achieved via forward and/or backward modes. The infective or transmissibility period of the case can be used to determine who the case might have infected ("to whom"), which helps in the identification of secondary cases and the construction of case generations. During home visits, information about how measles was contracted can be obtained (Whittle et al. 1999) for the classification of secondary cases if rash onset occurred 7 to 21 days post rash onset in the primary case (Hales et al. 2016).

To establish the source ("from whom") of the infection, identify additional cases and understand transmission patterns, travel history of the case during the incubation period is collected. Cases are interviewed about hospitals visited during the 7 to 21 days prior to measles rash onset (Zhang et al. 2015), contacts are monitored daily for symptom development up to 21 days post the last date of possible exposure (Ma et al. 2017) and suspected cases are asked for any travel in the 21 days prior to rash onset (Lemos et al. 2017).

Combined approaches involve obtaining the history of activities from cases 21 days prior rash onset up to 5 days post rash onset (Ma et al. 2016) and collecting information of all places visited by cases in 7–18 days before rash onset or during the period between the beginning of respiratory symptoms until 4 days after rash onset(Quiroga et al. 2003). In addition, simply collecting information on recent contacts without stating any timelines has been used (Goodson et al. 2010).

Contact Tracing Methods and Case Identification

Evidence would indicate that there is a link between shared space identification as a method of CT and identification of additional cases through CT. Four (Jin et al. 2011; Quiroga et al. 2003; Rathi et al. 2017; Sarmiento et al. 2011) out of the six studies that reported cases obtained through CT had considered everyone sharing an enclosed space with the case as a contact. One study (Sarmiento et al. 2011) reported 14 cases that were absent from surveillance records and uncovered 120 confirmed cases during a period which was initially thought to be epidemiologically silent. In addition, another study (Quiroga et al. 2003) identified 12 cases not present in surveillance records, the third study (Rathi et al. 2017) identified 9 additional cases which accounted for 45% of all cases in the outbreak, and the fourth (Jin et al. 2011) identified 112 additional suspected cases of which 9 were confirmed. Thus, shared space identification appears to be a more comprehensive CT strategy.

Economic Costs of Contact Tracing

None of the included studies determined the economic costs of CT separately from other outbreak activities but CT was incorporated into the costing of the entire outbreak. Consequently, costs will be analysed as per the study finding with highlights on CT when available. In addition, due to the perspectives and unit of costs being similar, it is possible to make comparisons where possible across the studies.

Contact Tracing Cost and Outbreak Magnitude

The total outbreak cost ranged from $0.4 million (Ma et al. 2017) to $5.5 million (Njau et al. 2019) and the cost per case from $144.35 (Wallace et al. 2014) to $18,000 (Ma et al. 2017) among the studies included in this review. In one study (Ma et al. 2017) where the cost/case was the highest, overall outbreak costs were lowest, with the lowest number (22 confirmed) of cases and shortest outbreak length (19 days) when compared to two other studies each having 6.5 months outbreak length with 409 cases (Pike et al. 2017) and 5257 cases (Wallace et al. 2014) respectively, or with another of 24 months outbreak duration and 12,427 cases (Njau et al. 2019). In this same study (Ma et al. 2017), CT was used extensively and expended 77.5% of provider time as part of outbreak response cost that formed the bulk of the total outbreak expenditure. This indicates that timely and robust CT may be effective (fewer cases, less severity of cases, no/less deaths, shorter outbreak) and could be good value for money.

The overall outbreak cost is a function of the comprehensiveness of the range of costs considered in cost analysis and the extent to which each response intervention was used. In one study (Wallace et al. 2014), seven measles deaths were not factored into the calculation of productivity losses and had an overall outbreak cost of approximately 0.8 million, which is just above the average cost estimate (≈0.6 million, without application of income elasticity) for the lone death in another study (Pike et al. 2017) with about 4 million total outbreak cost. Given that these two studies have similar outbreak lengths (6.5 months), the huge disparity in their overall outbreak costs could partly be as a result of differential cost inputs. Also, while the latter (Pike et al. 2017) specifically stated CT as part of outbreak response, the former (Wallace et al. 2014) used the umbrella term ‘active surveillance’ which could be indicative of minimal CT, and thus the reason for the variance in cost. Also, the extensive use of CT in another study (Ma et al. 2017) may explain its high ($18,000) cost per case.

Direct versus Indirect Contact Tracing Costs

For the health sector, direct labour costs tend to be the main driver of outbreak response costs. In the Romanian study (Njau et al. 2019), provider reimbursement for the treatment/management of cases was $3.3 million which is more than half of the 5.5 million spent in total for outbreak response. In the Micronesian study, labour cost constituted the main economic burden for the country (Pike et al. 2017). Again, 98.4% of outbreak control costs were from labour in a Chinese study (Ma et al. 2017).

For households, the indirect costs of workdays lost because of measles infection/death (either as a case or caregiver) dominated expenditure. For example, the opportunity costs of lost workdays accounted for 89.4% of the total household costs in one Chinese study (Ma et al. 2017). Similarly, 87% of household costs have been shown to be opportunity costs (Wallace et al. 2014).

Discussion

The aim of this systematic review was to identify methods used in CT and the associated economic costs. The 17 studies included in this review had varied research designs, making it impossible to conduct any form of meta-analysis. None of these studies compared CT to no CT, thus, no empirical data addressing the review question was found and it was not possible to determine the effectiveness of CT as compared to no CT in preventing measles spread during outbreaks in LMICs. Also, none of the included studies assessed CT or its costs separately. Disaggregation of data on CT and the paucity of studies on resources used in CT and associated costs has been previously identified (Canadian Agency for Drugs and Technologies in Health 2015) and could be explained by the insufficiency of CT when infection spreads rapidly and contacts increase exponentially (Dhillon and Srikrishna 2018).

Methods of Contact Tracing

The evidence would suggest that shared space identification was the most frequent method of CT and is associated with finding additional cases. A similar approach in CT is where contacts were located by identifying homes of hospitalised index cases (Mupere et al. 2006). Similar findings indicate that CT helps in identifying exposed co-workers and patients (Jones et al. 2015) as well as exposed individuals who have boarded the same plane as the imported case (Beard et al. 2011). Asking cases/caregivers to recall contacts was also common among the selected studies. This same approach was employed in the economic assessment of hospital-associated measles outbreaks in the USA, where suspected measles cases were interviewed for a list of contacts (Chen et al. 2011). This method is subject to bias as contacts unknown to the cases may continue to spread infection – if infected (Dhillon and Srikrishna 2018), and may not be investigated, thus limiting study findings (Ching, Zapanta, de Los Reyes, Tayag and Magpantay 2016).

With the index case as the focal point, CT can be done backward and/or forward to determine the source of the infection and onward spread by using the case's exposure and infective periods respectively. In the UK, the health protection teams use both perspectives by obtaining information on contact/travel history and close contacts (Smith 2018). Consequently, unprotected contacts have been advised to vaccinate or self-exclude for 21 days [the incubation period] and suspected cases isolated for 4 days post rash onset (Begum, Chow, Falola, Meltzer and Shah 2017), which corresponds to the infective period . Therefore, CT can be viewed as a continuum of "from whom" (backward) "to whom" (forward) and CT methods can be applied in either (forward or backward) or both directions.

Costs of Contact Tracing

Evidence from the included studies show that the cost per case of CT is high. The costs of investigating possible, probable and unreported cases has accounted for 67% of total outbreak costs with direct public health costs (CT inclusive), almost 1.5 times that of hospital admissions (Ghebrehewet et al. 2016). Provider labour costs/time is the main driver of high CT costs within

the included studies. This is not an isolated observation as staff absenteeism owing to lack of immunisation evidence, exposure or measles accounted for 56% of total outbreak costs during a hospital-associated outbreak (Chen et al. 2011). From the provider perspective, labour cost estimates of a single imported case of measles can range from $264 to $300 per contact (Coleman et al. 2012). Also, an estimation of the health sector economic burden of 16 measles outbreaks in the USA (Ortega-Sanchez et al. 2014) was at 42,635 to 83,133 personnel hours spent in tracing 8,936 to 17,450 contacts with an equivalence of annual full-time hours of 20 to 39 providers spent on investigating these measles outbreaks.

Evidence would suggest that if CT is initiated early (Ma et al. 2017), secondary cases can be prevented (Coleman et al. 2012), complications and deaths can be averted resulting in reduced overall outbreak costs (Ghebrehewet et al. 2016). Complications like encephalitis can require up to 8 months of rehabilitation (Suijkerbuijk et al. 2015) and the average cost of a measles case complicated by encephalitis is $50,500, $70,059 and $132,487 or $6,535, $9,173 and $9,544 for febrile convulsion complications in the Netherlands, UK and Canada respectively. This is far above $276, $307 and $254 spent on average per case for uncomplicated measles in these same countries (Carabin, Edmunds, Kou, van den Hof and Nguyen 2002).

The high disparity in outbreak response cost per case in the included studies could be explained by the corresponding difference in the contacts per case ratios which has been shown to have the highest impact on CT costs during sensitivity analysis (Canadian Agency for Drugs and Technologies in Health 2015). However, this rising CT costs per case can be mitigated if CT results in a short outbreak duration. This is because the extent of public health response is directly proportional to not just the number of cases plus contacts but to also the length of the outbreak with the mean costs of small outbreaks ranging from $2685 to $22,000, from $58,000 to $146,000 for medium outbreaks, and from $551,000 to $985,000 for large outbreaks (Ortega-Sanchez et al. 2014). This cost per case variance in the selected studies may also be as a result of case count differences ($18,000/case for 22 cases, and $ 439/case for 12,427 cases). This finding would concur with the evidence that public health response costs are inversely proportional to the number of cases in an outbreak and are a function of the number of contacts traced (Ghebrehewet et al. 2016).

In this systematic review, labour costs dominated health sector-related outbreak costs while household-related costs were driven by the opportunity costs of workdays lost by cases/caregivers. Evidence on measles outbreak and associated economic costs show that the health authorities bear most of the costs owing mainly to intensified surveillance, media communications, case registration workload and use of experts while productivity losses are partly attributed to childcare (Suijkerbuijk et al. 2015). In addition, there is substantial evidence that illness-related expenses are overwhelming and driving poverty among households in LMICs (McIntyre, Thiede, Dahlgren and Whitehead 2006).

From the included studies in this systematic review, the overall outbreak cost is influenced by the range of costs considered in cost analysis and the extent to which each outbreak response intervention is applied. It has been shown that the size of an outbreak affects the type and intensity of response and thus resources required (Canadian Agency for Drugs and Technologies in Health

2015). Evidence from the health sector perspective shows that outbreak response is not cost-effective (€524,735/QALY compared to the threshold of €35,500/QALY) for few preventable measles cases. However, this finding is only generalisable to countries that have achieved measles elimination (Ramsay et al. 2019) and therefore suggest that CT could be cost-effective in LMICs where the prospects of large measles outbreaks are high, and elimination has not been achieved.
In these unprecedented times of the coronavirus disease-2019 pandemic, a new highly infectious, droplet and contact borne viral disease, the WHO's provisional guidelines acknowledged the central role played by CT in outbreak investigations when implemented systematically and on time to break rapidly growing transmission chains. Across the different settings in which transmission can take place, the importance of interviewing cases to identify contacts is highlighted. Also, establishing lists of individuals (where possible) who have shared spaces with cases or warning/informing any potential contacts was emphasised (WHO 2020). These methods of identifying contacts were common across the studies included in this systematic review and reiterates the relevance of timely and organised CT efforts as the world prepares for a potential second wave of the coronavirus disease-2019 pandemic.

Limitations

Only four included studies evaluated the economic costs of CT and because CT was jointly costed with other outbreak response activities, it was difficult to determine what proportion of these costs were attributed to CT alone. Future studies should consider disaggregating data so that the direct and indirect costs of CT can be measured separately from the costs of other outbreak investigation activities. An update of this systematic review will also be needed as journal articles addressing the research question could not be found in the searched databases.
In addition, the findings of this systematic review are prone to bias. It is possible that only studies with significant results were published and thus selected for this review, introducing selection bias. Language bias could arise from restricting the inclusion of papers to only those published in English. There is also a potential for publication bias in this systematic review as grey literature was not reviewed.

Conclusion

To the best of our knowledge, this systematic review is the first to be conducted on CT methods and its associated costs in LMICs during measles outbreaks. Results indicate that there is a paucity of CT data as a standalone and comparative active surveillance approach in LMICs. Results also suggest that CT by recall and shared space identification are common during outbreaks in LMICs. However, CT based on contacts recalled by cases may not be very comprehensive compared to that by shared space identification. Using a measles case as a focal point, CT can adopt a backward or forward perspective or a combination of the two by using the exposure and infective periods of the case to determine who the case was exposed to, and who may have been exposed to the case. Thus, CT can be viewed as a continuum of "from whom" (source/backward) "to whom" (secondary cases or forward). Evidence suggests that the cost of CT per measles case is high, and

is dominated by labour expenses from the health sector perspective and productivity losses from the household perspective. The overall outbreak costs can be low if CT is timely and leads to a reduced outbreak size and/or duration. This will reduce the economic burden of measles and drive LMICs towards measles elimination. In this coronavirus disease-2019 era, it is important for governments to allocate sufficient CT resources to maximise the benefits of early and organised CT implementation should a second wave of the pandemic occur. This COVID-19 pandemic could increase the competition for the already endangered measles campaign resources with an associated increase in the risks of larger outbreaks in the future.

Abbreviations

CASP	Critical Appraisal Skills Programme
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CT	Contact Tracing
€	Euros
LMICs	Low- and Middle-Income Countries
PICO	Population Intervention Comparator Outcome
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	Prospective Register of Systematic Reviews
QALY	Quality Adjusted Life Year
QHES	Quality of Health Economic Studies
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
$/USD	United States Dollars
UK	United Kingdom
USA	United States of America
WHO	World Health Organisation

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Figure 1

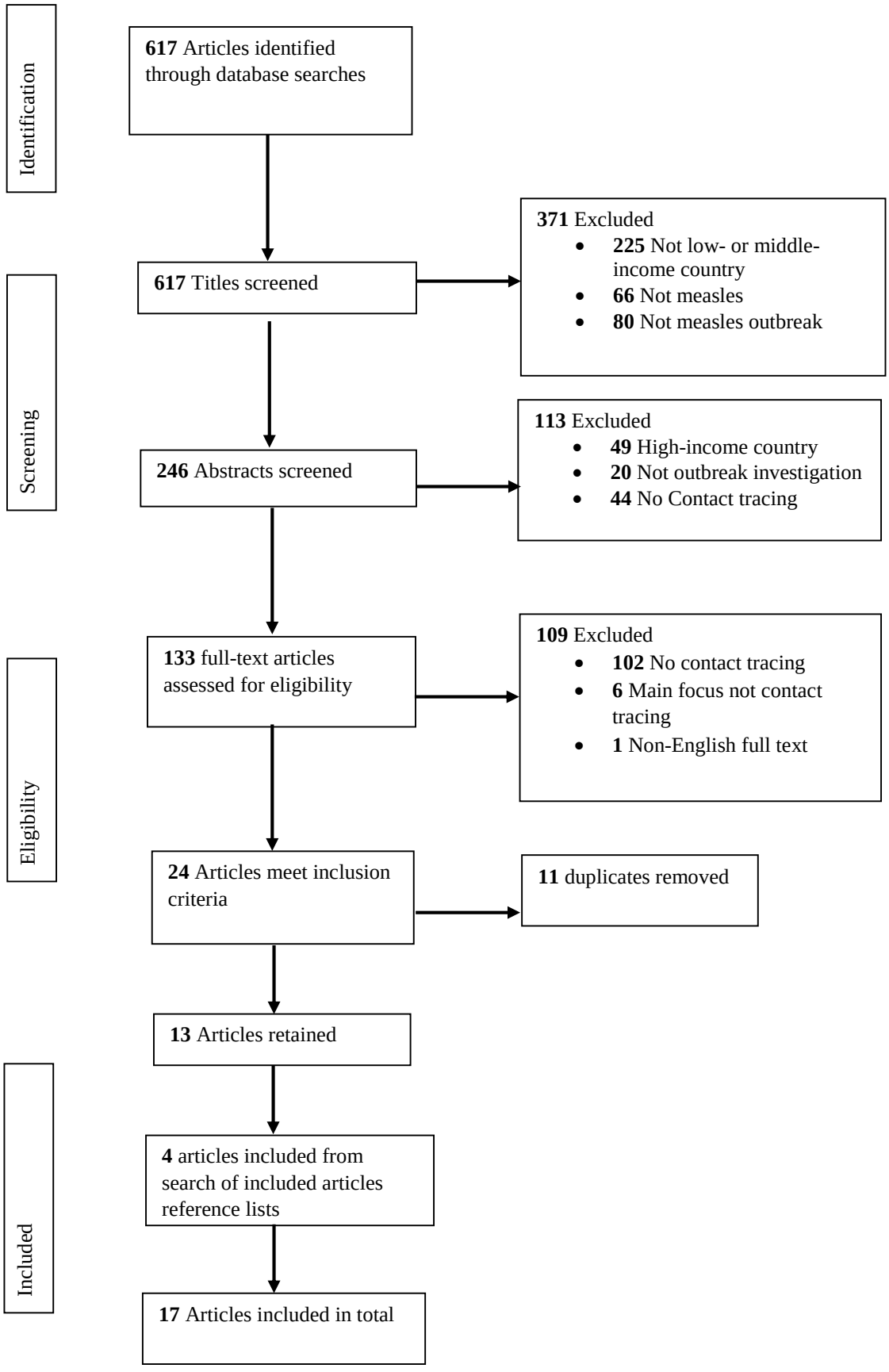

Fig. 1 Article Selection Process

Table 1 Keywords used in database searches

PICO Framework	**Keywords**
Population	low- and middle-income countries, developing countries, under developed countries, low resource countries, third world countries, global south, heavily indebted poor countries, and least developed countries.
Intervention	Contact tracing, case finding, case investigation, case search, rumour surveillance, contact management, contact investigation, and transmission chain tracking
Comparator	No contact tracing
Outcome	Measles outbreak control, measles outbreak termination, measles outbreak interruption, measles epidemic control, reduce measles spread and decrease measles transmission.

Table 2 Article Search Strategy

Boolean Operators	Search Serial Number	keywords	Database Hits					
			Global Health via CAB Direct	*PubMed*	*Cochrane Library*	*Web of Science*	*Cinhal via EBSCOhost*	*Medline via Web of Science*
OR	1	Low and middle income countr*	12,855	10,842	1,969	17,519	11,134	18,553
	2	Developing countr*	4,947,453	121,116	2,575	243,591	43,393	203,267
	3	Under developed countr*	512,553	118	341	23,671	169	17,272
	4	Low resource countr*	92,933	612	460	19,219	1,145	13,447
	5	Third world countr*	60,413	1,039	389	7,150	1,054	5,099
	6	Global south	69,584	32,827	543	40,738	1,387	10,326
	7	Heavily indebted poor countr*	19	3	2	53	9	5
	8	Least developed countr*	388,626	237	330	41,062	405	36,165
1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 = S 9			**4,960,362**	**159,400**	**6078**	**305,305**	**52,955**	**227,036**
OR	10	Contact tracing	2,836	5,612	921	10,746	2,468	8,524
	11	Contact management	10,460	27,925	5,642	25,182	2,327	16,748
	12	Contact Investigation	6,688	9,691	4,434	38,929	957	16,047
	13	Case finding	234,263	454,123	5,493	1,036,771	20,038	886,085
	14	Case investigation	45,563	63,672	3,271	178,194	6,346	133,874
	15	Case search	17,760	35,569	2,536	112,797	2,981	75,029
	16	Rumour surveillance	23	16	3	88	22	38
	17	Transmission chain tracking	208	127	78	368	3	250
10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 = S18			**290,908**	**574,524**	**16,328**	**1,292,133**	**32,910**	**1,047,366**
OR	19	Measles Outbreak Control	1,115	2,379	23	727	101	2,252
	20	Measles Outbreak termination	3	7	1	6	1	8
	21	Measles Outbreak interruption	35	57	1	36	1	63
	22	Measles epidemic control	631	838	17	391	23	760
	23	Reduc* measles spread	56	92	5	87	3	68
	24	Decreas* measles transmission	119	178	13	151	4	175
19 OR 20 OR 21 OR 22 OR 23 OR 24 = S25			**1,608**	**286**	**54**	**1,137**	**132**	**2,743**
AND	S9 AND S18 AND S25 = S26		**337**	**275**	**19**	**20**	**38**	**47**
Filters	1990-2019 English		260	244	18	20	38	38
Articles retrieved per database			259 (1 duplicate)	**244**	**18**	**20**	**38**	**38**

Table 3 Main Characteristics of Studies on Contact Tracing (CT) Methods

Author (Year), Country	Setting	Study Population	Research Design	Intervention	Intervention description	Outcome	Outcome description	Limitations and funding
Hales et al. (2016), Federated States of Micronesia	Lower MIC. Island Community (urban/rural mix).	1 death. 251 confirmed cases & their household contacts (Median household size=6.5 & median household number/room=4). 2013 1st & 2nd dose coverage 85% & 72%. Standard (professional body) case definitions. Contact = sharing meals or spending ≥1 night with primary case 3days prior - 3 days after rash onset. Outbreak length = 3 months,	Secondary attack rate (AR) study. Convenience sample. 80 primary cases & 580 contacts. Controls = unvaccinated exposed contacts.	Follow-up of 318 contacts [median age 14 (6months - 36 years), 157 females] for one incubation period post exposure.	Record review for primary cases. Interview of household members to confirm primary case & identify contacts. Contact follow-up ≥18 days. Treatment of unvaccinated contacts (n.d.)	Overall secondary attack rate, AR≈6% (18/318, 33% lab confirmed). VE for precampaign dose 23.1%, 63.4%, & 95.9% for 1, 2 & 3 doses regardless of campaign dose. VE of campaign dose was 78.7% & 50.4% for pre & post exposure doses irrespective of precampaign doses.	AR for 0, 1, 2, or 3 pre outbreak doses regardless of campaign dose is 13%, 11%, 6%, and 0% respectively, & is 9%, 1%, & 4% for contacts with no campaign dose, 1 pre & 1 post exposure doses respectively.	Small number of controls reduced precision of VE and AR calculations. Some cases not lab confirmed. Funding (n.d.)
Lemos et al. (2017), Brazil	Upper MIC. Community (urban/rural mix).	8.5 million 2014 population. Optimum (>95%) Vaccine Coverage (VC). Contact= anyone sharing enclosed space or living in same household during infective period of case. Standard national case definitions used.	Descriptive study of outbreak response (retrospective analysis of surveillance records & other documents). Convenience sample of households.	Contact tracing (photo of measles case used), vaccine coverage monitoring, expert meetings, weekly epidemiological reports, mass media communication, 50,000 samples tested, training of healthcare personnel	30 days follow-up of contacts, investigation of suspected cases & PEP for contacts ≥6months, household interview for VC, scanning vaccination, follow-up campaign, vaccine intensification, mass vaccination, information campaign (measles presentation & vaccine importance), expert meetings monitor outbreak & inform action, sample testing (measles & dengue, zika & chikungunya)	4631 suspected & 1052 confirmed measles cases in 38/184 cities in Ceara within 20 months (12/2013 to 10/2015). 90 days of close surveillance after last reported case confirms outbreak interruption. 11,410 contact vaccine doses given.	index & primary case implicated in nosocomial exposure/spread. integration & coordination of different response activities across different sectors & strict surveillance system ensure termination. Isolated PEP insufficient, inadequate resources & poor political will slows response. Tourists & overreliance vaccine coverage supports spread.	n.d.
Whittle et al. (1999), Senegal	Lower MIC. residents in huts grouped into households within compounds. Setting (rural &community).	Outbreak length = 12/1991 to 08/1992 ≈9months; age<7yrs; high, intermediate & low intensity of exposure = living in same hut, household, compound respectively. Clinical measles = 4 times increase in antibodies + symptoms; Subclinical measles = 4 times increase in antibodies + no symptoms. Definition for possible or not measles (n.d). 1992 VC 81%.	Design (not specified). Sampling (all routinely reported primary cases). Logistic regression	Contacts within same compound identified & traced from index case interview. Blood sample collection & antibody testing. 1 & 6 month follow up & treatment of secondary cases	cases identified by routine surveillance, contacts identified & traced through case interview. Blood sample collection at 1st visit (exposure) from cases & exposed, then at 1month (123 contacts) & 6-9 (90 contacts) months post symptom onset for sick & well contacts. symptom development checks ≥2 times/week for suspected cases in 1st month.	55 index cases (mean age 51 months), 51 compounds, 161 contacts (mean age 36 months). 17% & 42% developed clinical & subclinical measles respectively. No mortality. VE= 91%. Early case diagnosis & treatment (not specified)	56% of unvaccinated & 1% vaccinated developed clinical measles. 25% of unvaccinated & 45% of vaccinated developed subclinical measles. Older unvaccinated children with high intensity of exposure (same hut or household) are more likely to have clinical measles. Subclinical measles common among the vaccinated & increases with exposure intensity	N.d. on effect of exposure to subclinical measles. Funding: Medical Research Council; Task Force for Child Survival; Science & Technology for Development Programme
Goodson et al. (2010), Tanzania	LIC. Dar es Salaam (economic capital). Urban/community setting.	Outbreak length = 07/2006 - 01/2007 (8months); 1533 confirmed cases (most <2yrs). WHO standard case definitions. 2006 VC 93%.	Case-control study [cases (201) & randomly selected controls (200)]. Sensitivity analysis	interview of lab confirmed cases for contact history. Standard case investigation form used to collect data.	lab-confirmed cases provide names of recent contact for secondary case identification & epi-linkage. Treatment for lab & epi linked confirmed cases. Contact follow-up (n.d.)	68 epi-linked cases identified, 31/39 (91%) included in the study treated (vitamin A). VE = 88% & 96% for 1 dose & 2 doses of measles vaccine	Measles risk factors = age (<10), 0 or 1 vaccine dose & caregiver educational level.	Bias (recall, attrition,), missing data Funding: CDC; MOH, Tanzania; WHO.

Rathi et al (2017), India	Lower MIC. Town of both national & international university students. Community & school outbreak.	VC = 97.4%, WHO standard case & outbreak definitions used. Outbreak length = 1.5 months. Same or adjacent hostel/apartment residents considered as contacts.	Study design (not specified). purposive sample.	Interviews: residents, adjacent staff quarters residents, housekeeper & caretakers; investigation team contact provided; vaccination status check. Sample collection/testing. Isolation, treatment, follow-up; stakeholder meetings; hostel clinics; information campaign	Interview on symptoms. Interviewees contact investigation team for suspected cases. interview & card checked for case vaccination status. Sample collection/testing. Suspected cases isolated, treated with vitamin A & appropriate food, follow-up. Doctors & hostel warden meetings, investigation team meetings inform action, surveillance at hostel clinics & hospitals by night.	Outbreak length = 1.5 months; cases = 20 (50% 16-20 yrs, 70% males). 9/20 (45%) cases identified via CT. No deaths. Overall AR = 3.5%; VE = 75%.	540 contacts investigated (interviewed & blood samples collected). 9/540 contacts diagnosed (secondary AR = 1.67%). AR 7.8% in unvaccinated & 2.01% in vaccinated.	unassessed serology assay. Missing vaccination status data Funding (n.d.)
Jin et al. (2011), China	Upper MIC. Urumqi, Xinjiang capital. Setting (urban & community/school).	07/03-30/04 2008 (56 days, ≈ 2months). 8442 (3300 male + 5142 female, 8309 students + 133 staff/teachers). Citywide outbreak length = 11/2007-06/2008 (8 months), > 2700 cases (≈50 are College students). Operational case definition. 2004 VC 95%.	Case-control study [all (90) probable cases & random class/sex matched controls (150), ≈ratio 1:2]. Multivariate & univariate logistic regression done	Daily temperature & rash checks; isolation, follow up & testing of cases; hospital referral of probable cases for isolation, definitive diagnosis & treatment. Interview/questionnaire for cases & controls.	follow-up/observation of rash or fever cases for probable case conversion. Questionnaire for cases & controls or face-to-face interview on exposure history 2weeks prior to measles in case. vaccination history of cases & controls. ORI.	Overall AR = 1.9% (162/8442). Student AR = 1.9% (159/8309) & teacher/staff AR 2.3% (3/133). 112 additional suspected cases, 9 confirmed student cases by CT.	Suspected case (162; 159students + 3 teachers/staff, 90 male). Probable case = 99. confirmed case = 62. Risk factor= poor air flow in internet café (possible synergy with direct contact)	Role of vaccines, community transmission & direct contact not assessed Funding = Chinese CDC
Garenne and Aaby (1990), Senegal	Lower MIC. Setting (farming community/rural).	Study period = 4yrs (03/1983-12/1989). Length of outbreak (unclear). Average 14 people/compound, 8/household, 2.5/hut. Operational definition (measles death & post measles death); Importation (n.d.)	Study design (not specified). Sampling (all routinely reported cases). LOGIT regression & standardization	Yearly investigation of routinely reported & confirmed cases (from line list) to establish source (from parental report) & transmission pattern	doctor assesses routinely reported cases. Index case/compound identified from line list. Source of index infection & other cases identified via parental report. Follow-up and treatment (n.d.)	1500 cases (0-30yrs), 39.5% index, 60.5% secondary. ≈3.5 same compound children infected/index case. Overall, case fatality ratio = 65.3‰, overall post measles mortality = 32.8‰. Dose effect relationship.	risk of measles mortality ∝ intensity of exposure for same compound secondary cases. high intensity (hut/ house/compound), severity (dispensary) of exposure & high generation increased the risk of measles death.	lack of resources for lab confirmation of cases Funding = Unite de Recherche Population et Sante.
Ma et al. (2016), China	Upper MIC. mostly rural (195 villages). Community/hospital.	2012 VC = good (every birth cohort covered). Outbreak length 29/12/2013-19/06/2014, ≈6months (280 cases). Standard WHO case definitions used. Importation (unclear)	Study design (not specified). purposive sample (cases in 1st 2 months).	case interview (contact with other cases +places visited). Follow-up = activity 21 days prior to 5days post rash onset.	case (occurring in 1st 2 months) interviewed (contact with cases +places visited). Follow-up = activity 21 days prior to 5days post rash onset.	280 cases (130 through CT). 52.8% (140) males. 77.6% (220) ≥20yrs with <5% documenting vaccine reception. 5/83 imported, 13/83 family-acquired, 24/83 nosocomial, 41/83 community-acquired.	44 interviewed cases epi-linked. ORI for all (non-selective) staying near case. 44,023 individuals vaccinated.	Limitations = n.d. Funding = Chinese CDC.
Sarmiento et al. (2011), Venezuela	Upper MIC. Mostly rural. Community/hospital outbreak	≈ 97% 2007 VC. Contact = all persons sharing enclosed environments (like house) with case during infectious period (4 days prior and 4 days post case rash onset). Contacts 14 days prior to 7 days post case rash onset also considered. Operationalised case definitions used.	Study design (not specified). Sampling (proportionate to size, 6115 clusters).	Contact list established. Follow-up= 21days. Local & national situation rooms. Transborder response plans. PEP for all contacts. Blockade vaccination. Active case finding	Blockade/perimeter vaccination for every confirmed case. House-to-house case search, document review for cases, stakeholder (provider & community leaders) interview.	122 cases (32% 1-4 yrs, 30.3% 18-39yrs, 3.3% vaccinated), zero complications & no deaths. Outbreak length = 50 weeks (≈12 months). 51 compatible cases via active community search (14 not in records).	185 suspected cases through active case finding. Surveillance record review reveals 120 confirmed cases during silent period.	Limitations= n.d. Funding = PAHO

Quiroga et al. (2003), Bolivia	Lower MIC. Nationwide (urban/rural) outbreak. Community/hospital outbreak.	1994 VC = 96%. Case and contact definition (n.d.).	Study design (not specified). Sampling (unclear).	Active case search [Record review, Measles pictures, stakeholder (health, religious, military & school personnel, students, community members) interview]. Contact search. Public transport clinics. Provider training.	159,085 records reviewed & 83,978 stakeholder interviews. Contact search at case house, neighbourhood & places visited 7-18 days prior or time of symptom onset to 4 days post rash onset. Vaccinators search for cases. Measles pictures in doctor's offices. Emergency response plan	Outbreak length (>2.5years, ≈30months). 2567 cases (32/100,000). 55% cases <5yrs. Mortality = 4. 122 cases via CT. 1 case via active case search.	Populous & capital cities most hit. Active case search increase provider/lay awareness of measles, reveals 12 cases not in surveillance, backdates onset of outbreak in some communities.	n.d.
Marin et al. (2006), Marshall Islands	Upper MIC. high population density. Community (rural/urban mix) outbreak.	2001 VC = 80% & 40% for 1st & 2nd dose respectively. Outbreak length = 6months. case>800 (23%<1yr), 100 hospitalised, 3 fatalities. Standard WHO case definition. Contact = anyone staying with infectious case ≥1day.	Secondary AR study. Sampling (convenience) 72 households.	Home visit & household contact interview. Contact follow-up (n.d.). Review of contact vaccine records	Standard case investigation form used to collect data during contact interview.	39/785 (5%) secondary cases (median age=1.4yrs, 3months-35 yrs). VE= 92% and 95% for 1 and 2 vaccine doses respectively. PEP or treatment of contacts (n.d.)	785 contacts. household median size = 12, median number of rooms = 2, median number of room occupants = 5.5	Detection and selection bias. Funding = CDC.
Zhang et al. (2015), China	Upper MIC. Setting: hospital & urban	2013 VC >95%. Outbreak length ≈2.5months (20/12/2013-28/02/2014). National standard case definitions.	Case-control study [(20) random cases with sex/age matched controls (40), ratio 1:2].	Surveillance & record review. Contact interview. Case/control exposure history. PEP for 8336 selective (unknown or partial vaccination) contacts. Case isolation, strict screening/triage of fever patients.	standard case investigation form to collect case data. Contacts = healthcare providers. Contact or suspected case follow-up: (7-21 days prior rash onset). Case/control exposure (places visited & contact with other cases 7-21 prior case rash onset) history	45 confirmed cases [16 males, 41 adults (23-51yrs), 4<8months]. AR (8.9/100,000). Outbreak length ≈2.5months. Measles risk factor = visiting hospital & IV treatment room	56 suspected cases. contacts treatment not specified. Risk of acquiring measles 20 times & 11 times higher for hospital & IV room treatment attendees respectively.	Incomplete participant data, unrepresentative serosurvey sample & missing cases Funding = Chinese CDC.
Cisse et al. (1999), Senegal	lower MIC. rural (30 villages). School/community setting.	1995 VC (64% for 1-14yrs). 512 students (502 in study area). Mean age 11, 5-33yrs. community case median age =8 (5months -30yrs). Outbreak length = 9months (10/1994-06/1995) for community & 4months (01-04/1995) for school. Operational case definition.	Study design (not specified). Sampling (all primary cases)	index case identified by surveillance & treated (Vitamin A + antibiotics). Cases sorted among same & neighbouring compound kids. School registers & spot maps used. Interviews (measles vaccination or infection history). Isolation of cases	Doctor assesses (suspected), diagnosis & treats cases routinely reported by field workers. Cases sort in same & neighbouring compounds. Investigation of cases at schools. Isolation (pupil asked to stay home till illness was over).	20/30 villages affected. 209 cases (108males, median age 7.8, 5months-30yrs). No deaths, 1 stillbirth. Index cases (103), secondary cases (106). VE= 74% (compound exposure), 57% (school exposure).	school index case = 25, & secondary case=38. Secondary AR increase with intensity (compound to hut) & severity (vaccinated to unvaccinated index) of exposure.	Limitations= n.d. Funding: Task Force for Child Survival and Development; Science & Technology for Development Programme.

PEP: Postexposure Prophylaxis 1, MIC: Middle Income Country, LIC: Low Income Country, n.d.: no data, MOH: Ministry of Health, ORI: Outbreak Response Immunisation, AR: Attack Rate, VE: Vaccine effectiveness/efficacy, CDC: Centres for Disease Control and Prevention, PAHO: Pan American Health Organisation, VC: Vaccine Coverage.

Table 4

Table 4 Main Characteristics of Contact Tracing (CT) Cost Analysis Studies

Author (Year), Country	Setting	Study Population	Research Design	Intervention	Intervention Description	Outcome	Outcome Description	Limitations and Funding
Pike et al. (2017), Federated State of Micronesia	Lower MIC; Mix urban/rural nationwid; Community	393 confirmed & 16 suspected cases; Median age 24, 64%>19yrs; 2014 VC=80%; Outbreak length ≈6.5 months.	Economic impact/cost analysis study. Sampling (n.d.). Government and partner agency document review	Assessment of economic costs and economic burden (on nation) of outbreak.	Range of costs [Outbreak containment costs (contact tracing, mass vaccination, Prior febrile rash cases review, cold chain practices and vaccination records), direct medical and non-medical costs, productivity losses (human capital approach + average wage/day + VSL)]; Unit of costs (USD 2014); Societal perspective; Valuing costs (Government & partner agencies); Sensitivity analysis (one-way); Discount (3%)	Total costs ≈$4,000,000 ($10,000/case) largely vaccine-related (procurement & outreach); High economic burden ($847,742 spent nears 2016 education budget); Labour costs (99% vaccine outreach). Additional >$3 million for case importation	Containing costs (90%, $3.5 million); Direct costs (4%, $141,000), [medical ($42,000 hospitalisation + non-hospitalisation) & nonmedical costs ($99,000 specimen shipping/testing)] Productivity losses (6%, $249,549)	Costs excluded: travel costs and time lost in travelling, fringe benefits + payroll tax, costs related to virus exportation. Case wage proxies & donations. Funding (n.d.)
Njau et al. (2019), Romania	Upper MIC. Mix (urban & rural). Community	12,427cases; Outbreak length ≈24months. 34% sampled cases <18 years, 50% males; for ≥18 yrs. 2010 VC ≥95%, low in adults.	Economic impact/cost analysis study; Sampling = purposive. Case & health sector interviews+ reimbursement data.	Households and health sector direct and indirect costs measured. Household burden evaluation Economic costs = financial + opportunity costs.	Range of costs [household direct medical (consultation, medication, lab fees) and non-medical (transport, feeding, lodging) costs plus indirect costs (case/carer productivity losses valued in minimum wage/day + human capital approach); Costs of provider case treatment; outbreak response (contact vaccine) costs]. Sensitivity analysis (one-way); Unit of costs = USD 2013 value; Valuing costs: Ministry of Health. Societal perspective; Discount (3%)	Total household costs = $1.7 million ($133.84/case); healthcare provider costs=$3,275,757; Response costs $516,351 ($41.55/case). Total societal costs= $5.5 million ($439/case). Economic burden greater on households (30% monthly and 3% annual income spent). 36% cases borrowed medication/transport money	$888,338 & $779,917 = direct (medical/non-medical) & indirect household costs respectively. $66.87 & $18.23 median direct out-of-pocket expenditure for in & out patient care respectively. 11.45 & 7 median days of work lost by cases & carers. 10 mean school absenteeism days. 87% response cost lab-related, 17% contact & high-risk vaccines.	Costs excluded: VSL & opportunity costs of provider time diverted to outbreak Bias: recall + selection. Unrepresentative sample. Underestimation of provider claims. Funding: (n.d.)
Wallace et al. (2014), Ethiopia	LIC. rural/semi-urban. Community	cases = 5257 [2590 <5 yrs, 2645 (5–14yrs), & 445 ≥15 yrs]. measles deaths = 7. National 2012 VC 66%. Outbreak length ≈6.5months	Economic impact/cost analysis study. Convenience sample of districts and cases. Record review & stakeholder interviews.	Economic costs = financial costs + opportunity costs. Societal costs = household costs + health sector costs. Productivity losses = workdays lost times daily wage	Range of costs [household costs (financial+ opportunity cost of illness & treatment e.g productivity losses, transport, food, lodging, medication, service fee), health sector costs (outbreak investigation, hospital/community treatment, active surveillance, vaccination, vaccine service enhancement)]; Unit of costs (USD 2011); Societal perspective; Valuing costs (Ministry of Health). Sensitivity analysis(one-way). Discount (n.d.)	overall economic costs = $758,869 ($144.35/case) [opportunity cost$327,545 ($62.31/case) + financial cost $431,324 ($82.05/case)]. Societal costs (overall outbreak/response costs = 44% of Keffa's 2012 public health expenditure)	Active surveillance $117,302 ($22.31/case) and ORI $380,052 ($72.29/case). 42% and 19% of economic costs = ORI financial costs and case/caregiver opportunity costs respectively. $29.18/case household economic cost = 6% household median annual income	Costs excluded: VSL of 7 deaths, local NGO response, household opportunity costs for ORI Participation Small convenience sample. Bias: recall + selection. Funding: (n.d.)
Ma et al. (2017), China	Upper MIC. Urban setting. Group of connected office buildings.	6891 workers. WHO Standard case definitions used. 85% adults immune to measles. Outbreak length = 19 days. Contact = all workers in affected buildings + exposed hospital staff & community members.	Economic Impact/cost analysis and outbreak description (cross sectional) study. Sampling (n.d.) Investigation team lead and case interviews for costs	Contact interviews. Case isolation & testing. Active case search in buildings+ communities. PEP. Office clinics. Stakeholder meetings. Information campaign. Economic costs = direct & indirect household costs + outbreak response costs	Fever/rash cases isolated. Contact (8 months-49 years) PEP. Office clinics for PEP. Investigation team, companies & community meetings to report/share information. Telephone, mass/social media information campaign. Range of Costs [household direct (consultation, medications, transport,) + household Indirect (case/caregiver lost workdays + paid carer) + outbreak response (labour, transport, materials)]. Valuing cost (average 2015 hourly/daily company salaries). Unit of cost (2015 USD), Perspective (societal). Sensitivity analysis (n.d.). Discounting (n.d.)	Outbreak length (19 days). Median isolation time = 2 days for 90% cases. Cases=22, AR = 3.2‰. PEP received 1st day post case diagnosis. No secondary cases. Total outbreak costs = $400,000 ($18,000/case) Household cost= $13,298.3 ($604.5/case). Total outbreak response costs =$384,594.2 ($17,481.6/case). 77.5% of personnel time in CT.	Contacts = 7930 (2<6months, 32 = 8months-14 yrs, 7896 = 15-49yrs). case median age = 32, 12 males. No community/ hospital cases. No deaths, complications or hospitalisation. Direct household cost = US$1404.2 (US$63.8/case). Indirect household cost = 89% total household costs. response cost: 90.7% employer, 7.8% hospital, 1.5% community	Costs excluded: telephone costs, employer benefits, overhead expenses. Bias: recall. Overestimation of office contacts & transport-related contacts and some hospital contacts excluded. Funding: No external funding

PEP: Postexposure Prophylaxis 1, MIC: Middle Income Country, LIC: Low Income Country, n.d.: no data, VSL: Value of Statistical Life, USD: United States Dollars, NGO: Non-governmental Organisation, ORI: Outbreak Response Immunisation