Systematic Review of the Manifestations of Congenital Rubella Syndrome

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Systematic review of the manifestations of Congenital Rubella Syndrome

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Abstract

Congenital rubella syndrome (CRS) continues to cause disability among unvaccinated populations, particularly in the 62 countries yet to introduce rubella vaccine and in immunized populations with insufficient vaccine coverage to prevent transmission. We systematically reviewed the literature on birth outcomes associated with CRS to estimate the duration, severity, and frequency of combinations of morbidities. We searched PubMed, the Science Citation Index, and references from relevant articles for studies in English with primary data on the frequency of CRS manifestations for ≥20 cases and identified 65 studies representing 66 study populations that met our inclusion criteria. We abstracted available data on CRS cases with one or more hearing, heart, and/or eye defects following maternal rubella infection during the period of 0-20 weeks since the last menstrual period. We assessed the quality and weight of the available evidence using a modified GRADE approach. Most of the evidence originates from studies in developed countries of cohorts of infants identified with CRS in the 1960s and 1970s, prior to the development of standardized definitions for CRS and widespread use of vaccine. We developed estimates of undiscounted disability-adjusted life-years (DALYs) lost per CRS case for countries of different income levels. The estimates ranged from approximately 26 to 38 for high-income countries assuming optimal treatment and approximately 29 to 39 DALYs lost per CRS case in low- and lower middle-income countries assuming minimal treatment, with the lower bound based on 2010 general global burden of disease disability weights and the upper bound based on 1990 age-specific and treatment-specific global burden of disease disability weights.
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Glossary

Atrial septal defect (ASD)
Congenital rubella syndrome (CRS)
Disability weight (dw)
Disability-adjusted life-years (DALYs)
Global Alliance for Vaccines and Immunization (GAVI)
Global Burden of Disease Project (GBD)
Last menstrual period (LMP)
Life expectancy (LE)
Patent ductus arteriosus (PDA)
Pulmonic stenosis (PS)
Quality-adjusted life-years (QALYs)
Ventricular septal defect (VSD)
World Health Organization (WHO)
Years of life lived with disability (YLD)
Years of life lost (YLL)
Introduction

Gregg first recognized in 1941 that maternal rubella infection in pregnancy caused congenital cataracts and hearing disability,[1] which changed the clinical perception of rubella from primarily a mild infection in children to a serious disease in adult women with teratogenic effects. Over subsequent decades clinicians characterized congenital rubella syndrome (CRS) as the result of rubella infection early in pregnancy leading to congenital heart defects, including patent ductus arteriosus (PDA), pulmonic stenosis (PS) and atrial or ventricular septal defect (ASD, VSD), congenital cataracts, congenital glaucoma, hearing impairment, and/or intellectual disability.[2] A pandemic that began in 1963 in Western Europe then spread to North America tragically led to a relatively large birth cohort of CRS cases that supported detailed characterization of CRS outcomes and their relative frequencies.[3] One study estimated that congenital rubella affected approximately 1% of live births during the epidemic in metropolitan New York and women therapeutically or spontaneously aborted approximately 75% of the reported pregnancies complicated by rubella.[4] A prospective sero-epidemiologic survey of 500 pregnancies during the 1963-1965 epidemic at 11 different institutions across the US included 2.4% of pregnant women that reported clinical rubella infection, with approximately 1% of these occurring in the first trimester.[5]

First licensed in 1969 in the United States, rubella vaccine provides immunological protection from rubella disease in over 95% of recipients after a single dose.[3] By 2013, 131 member states of the World Health Organization (WHO) introduced rubella vaccine and global adoption of rubella vaccines continues to increase.[6] With confirmation of rubella and CRS elimination pending in the Americas and a rubella elimination goal in the European region, the countries yet to adopt rubella vaccine include those of relatively lower income states in the African, Eastern Mediterranean, South East Asian, and Western Pacific regions, in which the detection of and treatment for CRS disabilities remain limited.

Despite decades of study, no systematic review of CRS literature provides a synthesis of the outcomes associated with rubella infection in pregnancy, evaluates study limitations and assesses the weight of available evidence. Estimates of disease burden, for instance using disability-adjusted life-years (DALYs), require comprehensive information about the duration, severity, and frequency of combinations of morbidities caused by CRS. With the increasing adoption of rubella-containing vaccines supported by the Measles and Rubella Initiative and GAVI Alliance, rubella and CRS elimination continues to gain more attention, although no global estimate of the DALYs lost per CRS case exists.

The next section describes the methods we used to conduct a systematic literature review, informed by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidance,[7] and develop estimates of DALYs lost per CRS case for countries of different World Bank income group levels [8] using disability weights from the Global Burden of Diseases, Injuries, and Risk Factors Study 2010 (GBD 2010)[9] and GBD 1990.[10] The final section provides additional context related to the results and discusses limitations that may impact their utility.

Methods

We performed a search of the literature indexed in PubMed and the Science Citation Index (ISI Web of Knowledge) for papers in English using the terms “rubella” and either “congenital” or “maternal” and included up through July 17, 2013. We screened the records doubly and unblinded for potential relevance to outcomes of rubella infection in pregnancy and obtained full-
text articles for all articles for which we could not determine relevance based on the information obtained in the citation indexes. We excluded records as described in Figure 1, mostly due to lack of relevance (see eligibility criteria in Figure 1). We assessed full text articles doubly and unblinded for eligibility and screened the references of relevant full-text articles to identify records missed by the database search, which we subsequently assessed for eligibility.

We developed a spreadsheet for data abstraction iteratively, with all authors participating in the review of six articles. Two authors (EAS, KMT) abstracted the data from every paper and resolved any differences by consensus. The other authors reviewed a subset of articles for discussion of specific issues. We re-reviewed all articles following subsequent modification of definitions and addition of new data elements. The abstracted data included study characteristics (e.g. age at follow-up and method of lab confirmation), individual CRS manifestations, combinations of CRS manifestations, and a catalogue of study limitations.

Studies of birth outcomes following rubella infection in pregnancy use different definitions and clinical evaluation methods and criteria. We focused on characterizing well-defined CRS outcomes following maternal rubella infection within the first 20 weeks since maternal last menstrual period (LMP) that impose significant chronic disability, including confirmed cardiac defects (excluding undefined heart murmurs), cataracts, glaucoma, hearing and intellectual disability (including diagnoses reported as developmental delay and mental retardation). For cases with a major CRS defect, we also captured a wide range of rubella-associated manifestations important for clinical diagnosis that do not independently cause significant disability (e.g. meningoencephalitis, microphthalmia, nystagmus, purpura, retinopathy, hepatosplenomegaly, jaundice, microcephaly, and radiolucent bone disease) and indications of intellectual disability (e.g., reports of cerebral palsy, seizures, and behavioral abnormalities.)[2]

Recognizing that the timing of the maternal rubella infection since LMP impacts the likelihood and severity of CRS defects,[11, 12] we abstracted available data related to the timing of the infections. Based on recommendations from the American Academy of Pediatrics to use the term “gestational age” as “the time elapsed between the first day of the last normal menstrual period and the day of delivery,”[13] we characterized gestational age at the time of maternal infection as the time elapsed since LMP. For studies that reported the time elapsed since conception, we added 2 weeks to estimate the timing since LMP. For studies lacking specifications with respect to the starting point used we used the definitions in other publications by the same author when available or assumed the reported gestational ages reflected time since LMP and noted the lack of information as a limitation.

We also recognized that studies provided different types of information depending on the extent to which they included laboratory confirmation. Specifically, in our iteration to develop the data abstraction tool, we found that following the successful isolation of rubella virus in 1962,[14, 15] researchers increasingly began to use laboratory testing to confirm maternal rubella infections and/or infants and to confirm CRS diagnoses using antigen or antibody detection, and/or virus isolation techniques. We considered the type of confirmation used. For example, antibody detection in adults, which represents the most common form of confirmation, requires a sera sample collected within four weeks of symptom onset to detect IgM or paired sera samples in order to detect a rise in IgG level to distinguish acute primary infection from immunity due to previous infection and this makes retrospective confirmation of maternal infection after the birth of an infant with CRS-like disabilities unlikely. Confirmation of congenital rubella infection can occur after birth of the infant, but these tests depend on sample collection from the infant prior to the point at which post-natal rubella infection might interfere. Consequently, we omitted laboratory results for tests administered after five years of age due to the high likelihood of
positive results associated with rubella infection in the child.[16] Studies of children born in the late 1960s often submitted a subset of cases to the laboratory for confirmation, presumably due to the cumbersome nature and expense of early laboratory methods. More recent studies generally include laboratory confirmation of infant rubella infection. We abstracted information to characterize whether or not each study included >50% of cases with laboratory confirmation using sufficient methods.

Study design choices related to follow up time of infants after birth impact the detection of CRS cases, so we also abstracted information related to follow up time. For example, observations of hearing impairment may not occur until the child fails to develop speech.[17] For studies that evaluated cases only for the first two years of life, we included cases with laboratory confirmed maternal or infant infection (when possible) and any defect associated with CRS, whereas we only included cases with one of the three classic CRS manifestations for studies that evaluated cases beyond 2 years of life. When the study authors did not explicitly report the age at follow-up, we estimated the ages of the earliest and latest possible ages of follow-up for each study based on the available information. We excluded neonatal deaths from birth outcomes to allow comparison with studies that recruited participants retrospectively (i.e., after neonatal deaths occurred). Consequently, this review provides insights related to outcomes of CRS for infants that survive the neonatal period (i.e., excluding spontaneous or therapeutic abortions, stillborn births, and neonatal deaths).

We based our characterization of the study limitations on existing approaches for assessing the quality of evidence. Designed primarily for the purposes of evaluating evidence from randomized control trials (RCTs), the GRADE approach provides a useful framework for interpreting study limitations and the quality of evidence.[18] We used the same overall framework for interpreting study limitations and the quality of evidence, but adapted the limitations to accommodate the nature of the CRS literature, which primarily provides observational data obtained using disparate methods of case ascertainment, follow-up, and lab confirmation techniques. We evaluated four main aspects of the studies: 1) design and methods, 2) quality of outcomes data collection (i.e. study execution and clarity and completeness of reporting), 3) direct relevance of the reported outcomes to measures of interest for this review, and 4) consistency of outcomes across studies. We used an iterative process to identify the critical limitations within each of these categories (including re-review of articles as appropriate). Table 1 provides the complete list of limitations that affect the quality of evidence and notes several limitations that we applied as exclusion criteria for quantitative analyses. Table 1 also shows the subjective weights we assigned by consensus to each study limitation to reflect our interpretation of its impact on data quality.

We characterized overall study designs according to the likelihood of obtaining an unbiased sample of infants with congenital rubella infection. We classified studies as:

- rubella infection in pregnancy identified prior to birth and birth outcomes followed up prospectively for all infants, including asymptomatic cases (i.e., prospective maternal cohorts)
- rubella infection in pregnancy assessed after birth and birth outcomes followed up for all infants, including asymptomatic cases (i.e., retrospective maternal cohorts)
- mixed recruitment based upon either rubella infection in pregnancy assessed prior to birth or clinical presentation of cases after birth (i.e., mixed cohort/series)
- cases identified based on clinical presentation after birth (i.e., infant case series)
- chart review of patients with suspected or confirmed CRS and/or review of institutional records from facilities serving disabled populations
• CRS surveillance, including registries of birth defects
• surveys of doctors, institutions, or parents, seeking information on the outcomes of rubella infection in pregnancy and/or CRS

We considered infant case series with CRS diagnosis supported by detection of rubella infection in pregnancy or infants after birth for >50% of cases as adequate for quantitative analyses. We excluded from quantitative analysis any studies that recruited participants based on a specific characteristic, such as children recruited at a school for the blind or deaf, and studies that failed to assess one or more of the triad of cardiac, eye, and ear major defects. When multiple studies presented the same population of cases we selected the study with the best quality of evidence score for the quantitative analyses to avoid double counting the individuals in the cohort in cross-sectional analyses.

We evaluated the proportion of cases with single manifestations and manifestations in combination by study design, duration since maternal LMP, and age at case examination. Given the limited sample sizes and methods, we only pooled studies with similar designs. We stratified the data according to the age at physical examination and we report disaggregated data on combinations of defects for studies with different designs and specified the limitation weight for each study.

To measure the impact of CRS on population health in DALYs, we characterized the severity of major defects in relation to health states evaluated by the GBD 2010[9] and GBD 1990.[10] We mapped the severity, frequency, and co-morbidity combinations to disability weights, assuming combined weights for two or more defects equals one minus the products of one minus each disability weight. To account for differences between treatment standards and access to care between countries, we estimated the approximate DALYs per CRS case by World Bank income group level (low, lower middle, upper middle, and high based on GNI per capita)[8] using disability weights, assumptions about the percent of cases treated, and life expectancies from the United Nations Population Division.[19] Consistent with the GBD 2010, we do not apply age-weighting[20] and for this analysis we also do not discount our estimates.

We characterized the DALYs lost as:

\[
\text{DALYs lost} = YLL + YLD
\]

Where YLL refers to years of life lost (i.e., mortality) and YLD refers to years of life lived with disability (i.e., morbidity). Since CRS presents with a wide range of health states (i.e., combinations of comorbidities), we expand equation 1 to the following:

\[
\text{DALYs lost} = \sum P_{hs} * YLL_{hs}(m_{hs},LE) + \sum P_{hs} * YLD_{hs}(d_{hs},LE)
\]

where we sum over all of the health states and for each health state (hs), \(P_{hs}\) represents the proportion of cases, \(YLL_{hs}\) represents the years of life lost (which depend on the mortality rate \(m_{hs}\) and the life expectancy (LE) minus age at death), and \(YLD_{hs}\) represents the years lived with disability (which depend on the disability weight \(d_{hs}\) times the remaining life expectancy at onset of the health state). We assume population weighted averages of 59, 65, 73, and 78 years for life expectancy for low-, lower middle-, upper middle-, and high-income countries, respectively.[8, 19]

Results

Overall evidence

We found 66 study populations that met the eligibility criteria for demonstrating the frequency of manifestations of CRS.[1, 11, 12, 17, 21-81] One article reported on two distinct cohorts
examined at different ages using different methods, which we treated as two separate study populations.[38] The last column in Table 1 summarizes the frequency of our observations of each limitation in this group of studies. Overall, we identified significant limitations for many of the studies, with the total limitation score exceeding 10 for 30% of study populations. We identified retrospective evaluation of rubella infection in pregnancy outcomes as the most common limitation (89% of study populations), which biases the outcomes toward more severe CRS cases.

Table 2 summarizes important characteristics of the study populations we reviewed, including the extent of laboratory testing performed to verify the rubella infection in pregnancy and/or congenital infection. We found that 58% of study populations (38/66) included laboratory confirmation techniques and confirmed congenital infection for ≥50% of CRS cases. The remaining studies occurred prior to the availability of lab testing, failed to report the methods used and/or frequency of lab confirmation, and/or confirmed a small subset of the cases presented. We encountered significant challenges with respect to characterizing and categorizing the laboratory information given the wide range of methods and ages of testing for suspected CRS cases. Only one study reported on laboratory confirmed maternal infection tested during pregnancy for all CRS cases.[11] Three studies reported laboratory confirmed rubella infection in pregnancy for <50% of CRS cases,[27, 30, 59] and two additional studies provided the results of maternal antibody tests after birth for the mothers of infants with suspected CRS, although maternal testing after birth cannot conclusively determine rubella infection in pregnancy.[37, 58] We found 38 of the remaining 60 study populations reported a history of rash and/or physician-confirmed rubella infection in pregnancy for at least 50% of CRS cases.

We organized Table 2 by study type, and reported on the age at physical exam, reported frequencies of CRS outcomes, and limitation scores. Approximately half of the studies reported the results of infant case series, which provided more limited information about the birth outcomes than studies that followed up rubella infection in pregnancy. We found relatively high limitation scores associated with studies derived from infant chart reviews, surveillance, and surveys, which led us to exclude them from quantitative analyses. The study type tended to correlate with limitations on design and methods for the majority of study populations. For example, prospective maternal cohorts allowed prospective infant data collection. In contrast, chart reviews evaluated maternal and infant outcomes retrospectively. The last column in Table 2 notes the study populations that we excluded from quantitative analyses due to their recruitment of participants from a specific group (n=14) (e.g., children at a school for the blind or deaf) and/or their failure to assess one or more of the major CRS manifestations (n=6). We identified 23 studies covering 16 populations as suitable for quantitative analyses (limitation scores ≤10 and maternal cohort designs, mixed cohort/series, or infant cases series with >50% of cases lab confirmed).

Two large national infant studies from the early 1960s identified CRS cases prenatally and provided large samples of CRS cases. The UK Public Health Laboratory Service initiated a prospective study on the effect of immunoglobulin given as post-exposure prophylaxis to approximately 30,000 pregnant women exposed to rubella between 1956 and 1966.[22, 23] The first study published on this UK population in 1967 did not include lab confirmation due to the unavailability of methods.[22] but a later study included an assessment of the seropositivity of children at ages 1-4 years old born following clinically diagnosed maternal rubella infections and confirmed the seropositivity of most children with manifestations consistent with CRS.[23] The US National Institute of Neurological Diseases and Blindness (NINDB) also studied a prospective cohort of CRS cases under its Collaborative Perinatal Project (CPP), which focused
on recruiting women for follow up of outcomes in early childhood related to risks experienced in the perinatal period (i.e., between 20 weeks of pregnancy and 28 days after birth). This prospective, multi-disciplinary study included pregnancies identified by 11 participating institutions between 1959 and 1966, with participants enrolled as early as possible during pregnancy (although nearly all joined the study after their first trimester).[82] The nation-wide rubella epidemic in 1963-65 in the US led to prenatal rubella exposure of a large number of enrolled infants. The publications linked to the project that met our eligibility criteria presented cases from a single institution and frequently combined the prospective CPP data with data on infants diagnosed after birth (i.e., outside of the CPP).[28-30, 33, 34] Two additional 1963-65 US infant populations in the US (not affiliated with the CPP) provided extensive evaluation of CRS cases in Houston[51, 52, 83] and New York.[31, 32, 84] Three countries account for over 65% of the studies in the database: the United States (25/66, 38% of study populations), the United Kingdom (10/66, 15% of study populations), and Australia/New Zealand (9/66, 14% of study populations).

Overall, the study populations represent 15 countries and 1 region (the European Economic Community), with multiple studies reporting on potentially overlapping study populations, which we designate as series A through J in Table 2. Some study populations considered series that overlapped by location and years of birth, but did not capture the same individuals overtly,[25, 53];[37-39];[11, 71];[74, 75] while other series aimed to provide new information (specific aspects of a larger cohort or updated outcomes at an older age) on a previously described cohort.[1, 35, 36];[22, 23];[28-30];[51, 52, 83];[31, 32];[43, 44] Unlike long-term follow up of many large epidemiological cohorts, these series failed to report sufficient detail to support the characterization of the long-term outcomes as a function of early outcomes. We could not reconcile the results of any of these study populations to create a single longitudinal cohort, due to unclear reporting on loss to follow-up and the incorporation of new cases in the cohort over time. The longest follow-up of cases, series F in Table 2 describes the first cohort identified by Gregg[1] and presents a long-term account of an infant case series re-examined periodically through 60 years of age, but with no laboratory confirmation and inconsistent inclusion of patients in the cohort.[1, 35, 36, 85, 86] The follow-up studies noted approximately 75% of cases able to work or take up home duties and 25% relying on social services by age 50.[35, 36] Diabetes mellitus affected 5 of 44 cases by age 29,[85] 5 of 40 cases by age 50,[36] and 7 of 32 cases by age 60,[86] (with treatment at the last follow-up reported as insulin in 3 cases, oral agents in 1 case, and diet alone in 3 cases). This represented a relatively high number of cases with diagnosed diabetes for the cohort compared to the general population in Australia (15% vs. 4%).[87]

Impact of the period of observation and timing of rubella infection in pregnancy

The studies we used for quantitative analysis reported varying levels of disaggregation of outcomes, with most providing the number of cases with major defects without indicating combinations of defects or the timing of rubella infection in pregnancy since the LMP. Figure 2 shows the relative frequencies of CRS manifestations for the non-excluded study populations for studies that included laboratory confirmation and physical exams both during infancy, which capture congenital cardiac and eye defects, and later in childhood, which capture hearing and intellectual disability.[11, 27, 30, 31, 38, 47, 50, 51] The results in Figure 2 illustrate significant variability in outcomes among these studies, particularly for eye defects and intellectual disability. Specifically, the results from maternal cohorts in Table 3 suggest that approximately 70%, 30%, 15%, and 30% of cases experience hearing impairment, heart defects, eye defects, and intellectual disability, respectively. In contrast, mixed cohort/series and infant case series indicate 10% more cases with hearing impairment, nearly twice as many cardiac defects, three
times as many eye defects, and intellectual disability in up to 50% of cases, which most likely occurs due to recruitment of more severe cases in infant case series compared to maternal cohort studies.

Table 4 summarizes the results of two studies with prenatal enrollment that provided data on the frequency of combinations of the three major CRS defects (hearing, eye, and heart) by timing of the rubella infection in pregnancy since the LMP.[11, 12] These studies and the overall literature show higher frequencies of cardiac and eye defects for rubella infection in pregnancy at 0-8 weeks since the LMP (21/37 cases) than at 9-16 weeks (8/36 cases). Hearing disability alone occurs relatively less frequently at 0-8 weeks (16/37 cases) than at 9-16 weeks (28/36 cases). The studies show similar numbers of infants affected by CRS following rubella infection in pregnancy at 0-8 weeks and 9-16 weeks, but only 1 case of CRS reported for rubella infection in pregnancy at 17-20 weeks since the LMP. Figures 3a and 3b show a cross-sectional view of the retrospective cohorts and case series with the fewest limitations, respectively, by age at case examination. These figures reveal the greater likelihood of detecting hearing defects after 2 years of age (≥90% of CRS cases) than before 2 years of age (10-80% of CRS cases).

Studies that report on outcomes detected during the first two years of life report proportionately more cardiac defects (26-80% of CRS cases) than those studies that report on children over 2 years old (4-55%), which for infants with cardiac defects may reflect successful surgical repair or death. A prospective maternal cohort reported the same trend after following up the same study population at a median age of 2 and 6-8 years (series A).[22, 23] The study reporting on outcomes at 2 years of age reported cardiac defects for 13 of 50 CRS cases,[22] while the follow up study at 6-8 years of age did not mention cardiac defects, although it revealed 7 new cases of deafness among 49 children previously identified as seropositive with normal hearing.[23]

Characterization of hearing disabilities

Two studies suitable for quantitative evaluation distinguished between unilateral and bilateral hearing impairment with a ratio of bilateral to unilateral impairment of approximately 7.4:1 (i.e., 59:8 cases).[23, 50] In the 6 other studies not considered suitable for quantitative analyses, the ratio becomes more exaggerated (i.e., 11:1 or 321 bilateral: 29 unilateral).[35, 39, 41, 59, 64, 74] Bilateral impairment generally implied severe to complete sensorineural deafness. One study reported profound hearing disability for 67% of cases for which the development of speech and language appeared very unlikely, even with specialized care.[70]

Characterization of congenital heart defects

We found detailed information about cardiac defects for 6 study populations included in the quantitative results that examined cases within the first two years of life.[27, 30, 31, 47, 61] Combined, these studies report 321 cases with heart defects with 308 specific defects and 86 unspecified defects out of a total population of 595 cases. The 308 specific defects include patent ductus arteriosus (PDA) in 145 cases (47%), pulmonary stenoses in 139 (45%) and atrial and ventricular septal defects (ASD/VSD) in 24 (8%). These studies did not report the number of cardiac defects per case, although cases can experience more than one defect. Given the small number of cases with ASD/VSD, we did not account for these defects and we assumed equal proportions of PDA and stenosis for cardiac defects to calculate disability weights. PDA requires cyclooxygenase (COX) inhibitor therapy (i.e., ibuprofen and/or indomethacin) and surgical intervention for approximately one-third of cases that do not respond to COX inhibitors.[88] PDA ligation represents a relatively safe procedure, leading to approximately 2% operative mortality after initial development of techniques in 1938,[89] to essentially no mortality
associated with treatment now,[90, 91] with no detected overall mortality by age 5[92] and mild functional capacity limitations in developed countries.[93] One study reported 8/21 (38%) cases of pulmonary stenosis required intervention.[45] Treated cases may experience operative mortality of 3-6% and a post-operative mortality of 4-5% by 25 years after surgery.[94, 95] Cardiac defects that require surgery but remain untreated (e.g., in resource-limited settings) increase mortality risks.[96]

**Characterization of eye defects**

We found details about eye defects reported for 7 study populations included in our quantitative analyses representing 637 cases.[30, 31, 39, 50, 52, 57, 61] Six study populations reported on cataracts, which occurred in 222/567 (39%) cases, with 57% bilateral (126/222) and 43% unilateral (96/222).[31, 39, 50, 52, 57, 61] Unilateral cataracts may permit greater functionality, but bilateral cataracts may respond better to surgical intervention, resulting in mild vision impairment compared to moderate impairment for unilateral cataracts following surgical intervention.[97] Four studies reported congenital glaucoma,[30, 31, 52, 61] which occurred in 23/534 (4%) cases (11% of the 197 cases with eye defects), but they did not report the number of cases of glaucoma that occurred in children with cataracts. Studies suggest that secondary glaucoma tends to occur in cases with cataracts[17] or follow cataract aspiration.[34] Both glaucoma and cataracts require surgery in children, with both conditions representing complications of surgical intervention of the other complication.[98-100] In the absence of clear information about the interaction of the conditions and the high likelihood of only detecting one eye disorder at a given point in time, we assumed independence of these eye defects and that both conditions result in equivalent morbidity.[101, 102] With the surgical techniques available in the 1960s in the US, cases with cataracts treated at an international referral center experienced significantly reduced visual acuity[41] and treatment resulted in "useful vision" in only 3 of 31 cases in another study population.[39] Current surgical techniques in developed countries can result in good vision with minimal or no need for correction with eye glasses, while in developing countries visual acuity remain severely impaired in more than 20% of cases post-operatively.[102] A recent study on CRS cases with eye defects and access to treatment in Oman, suggested moderate average vision impairment following optimal treatment for unilateral defects and severe average vision impairment for bilateral defects.[75] For untreated bilateral cataracts, limited evidence suggest severe visual impairment to blindness in half of cases and moderate visual impairment in the other half of cases by 4 months of age in developing countries.[103, 104] Even with treatment, up to 40% of congenital cataracts may lead to post-operative visual impairment and blindness in a developing country setting.[105]

**Characterization of intellectual disability**

Seventeen of 23 study populations included in our quantitative analyses reported on intellectual disability (see Table 2). Given the difficulty of assessing the severity of intellectual disability in children with profound hearing and/or visual impairment[49] and the inconsistent definitions and evaluation criteria used across studies, we observed highly variable results with respect to the role of intellectual disability in CRS across all 17 studies. Only 4 studies reported manifestations by morbidity combination and evaluated cases beyond the first two years of life when tests and observation more reliably reveal intellectual disability (see Table 5).[37-39, 50] Due to the potential for overlap between three studies populations (series G),[37-39] we included only larger of these studies[39] in the results reported in Table 5. Intellectual disability frequently occurred in combination with hearing and eye defects (32/40 cases of intellectual disability, or 28% of 115 total cases). In one study population with 83 CRS cases, 24 of 32 cases with intellectual disability required residential care for the intellectually disabled.[39] Two
other studies, not included in Table 5, reported an IQ of <70 for 12 out of 111 total cases.[49] and 20 of 69 total cases.[30] One study that reported on 10 CRS cases found mental deficiency as the “most serious anomaly” and noted distress that the study revealed 4 cases of severe mental retardation unsuspected in infancy.”[106]

**Mortality**

We found limited information about mortality reported in these studies. Table 6 summarizes any infant and child mortality reported in the studies we considered eligible for quantitative analysis (10 of 23 studies). Prospective maternal cohort studies reported lower child mortality (5% at ages 0-3 years, 9% at ages 0-11 years)[11, 12] compared to mixed cohort/series and infant case series (6-31% across multiple age ranges from 0-1 years to 0-7 years).[30, 31, 38, 47, 52, 57, 61] This observation most likely reflects the recruitment of more severely affected individuals in infant case series. These studies reported cardiac defects as the most common specified cause of child death, leading to 5/5 deaths in 54 cases[12] and 5/7 deaths in 33 cases.[57] Two additional studies reported heart defects as a cause for 5/5 deaths in 20 cases,[76] and 6/9 deaths in 34 cases with eye defects.[34]

Evidence suggests that increased mortality in adults with disabilities, and we see some evidence of this despite very limited follow-up studies that involve CRS cases. Repeated studies of an Australian study population showed 7/40 (18%) cases died between 25 and 50 years of age (during 1965-1990)[36] and 3/29 (10%) cases died between 50 and 60 years of age (during 1990-2000).[86] For comparison, less than 1% of the general population of Australia died between 25-49 years of age and 2.6% died between 50 and 59 years of age during equivalent time periods.[19] Cardiac defects continued to cause premature death,[36] along with a range of other causes, including accidents,[51] pneumothorax and bacterial sepsis,[34] and cancers.[36] Intellectual disability and sensory impairments also appear likely to contribute to higher than expected adult mortality. Data on cohorts born in Finland in the early 20th century suggest that mild intellectual disability in the absence of modern medical care may lower life expectancy by 14 years compared to the general population, although these conditions may not contribute significantly to premature mortality in contemporary optimal treatment settings.[107] Cataract, vision impairment, and hearing disability also appear to increase mortality risks among adults, even in optimal treatment settings,[108-110] with dual sensory loss implying greater mortality than hearing or vision impairment alone.[111] The modification of the impact of these impairments on mortality by cardiovascular disease, neoplasm, and lifestyle factors[108, 110] limits definitive synthesis of adult mortality for CRS cases compared to the general population.

**Mortality reduction and disability weight assumptions for CRS cases**

Using the context provided by our review, we characterized survival and disability weights based on both the GBD 2010 and the GBD 1996. To account for mortality early in life, we assumed that cardiac defects represent the sole cause of child death attributable to CRS, and we assumed a mortality rate (m) of 60%[112] for infants with PDA and 24% of infants with pulmonary stenosis die in their first year of life if untreated, while treatment (surgery) reduces the mortality risks to 0% for PDA and 1.2% within the first year of life and 1.6% within the first 5 years of life for pulmonary stenosis.[94, 95] To account for the likely increase in premature adult mortality, we assumed an overall reduction in life expectancy of 20% with no treatment and 10% with optimal treatment for all CRS cases with more than one defect.
To calculate an appropriate disability weight (dw) for hearing disabilities, for the GBD 2010 we assumed complete deafness (dw=0.033) for the 85% with bilateral disability and moderate deafness (dw=0.023) for 15% of cases with unilateral disability, regardless of treatment. For the GBD 1996, we used the age-specific weights for deafness for 0-4 year olds for untreated (dw=0.233) and treated (dw=0.175) cases. For cardiac disabilities (PDA and pulmonary stenosis), for the GBD 2010 we assumed that cases left untreated that survive experience “moderate heart failure” (dw=0.07), while cases treated optimally that survive experience “mild heart failure” (dw=0.037).[9] For the GBD 1996, we used the age-specific weights for congestive heart failure for 0-4 year olds for untreated (dw=0.323) and treated (dw=0.171) cases. For the GBD 2010 weights, we assumed severe vision impairment (dw=0.191) for untreated unilateral eye disabilities and moderate vision impairment (dw=0.033) for treated unilateral eye disabilities, and complete blindness (dw=0.195) for bilateral defects, independent of treatment. For the GBD 1996, we used the age-specific weights for congestive heart failure for 0-4 year olds for untreated (dw=0.037) for cataracts for untreated (dw=0.6) and treated (dw=0.493) cases for bilateral eye disabilities and age-specific weights for 0-4 year olds for corneal scar low vision (dw=0.223) for treated and untreated unilateral eye disabilities.

Multiple handicaps tend to diminish individual coping mechanisms for living with each handicap, and increase the level of treatment and institutional care required beyond that expected from a simple combination of single handicaps. Thus, children with blindness can compensate to some extent by relying on hearing, but children with blindness and complete hearing and/or intellectual disability can use fewer compensatory mechanisms and require more assistance with each.[39, 51, 70] For cases with combined hearing, eye, and intellectual disabilities, for the GBD 2010 disability weights we assumed one level higher severity than for cases with a single defect (i.e. we assume weights for complete deafness and blindness for hearing or visual impairments combined with each other and/or combined with intellectual disability). Our results only included intellectual disability combined with at least one other defect. For the GBD 2010, we used the weight for moderate traumatic brain injury (dw=0.224) for combinations of comorbidities that included intellectual disability and hearing or eye alone or with cardiac disability, and we used the weight for severe traumatic brain injury (dw=0.625) for combinations of comorbidities that included hearing, eye, and intellectual disabilities. For the GBD 1996, we used the age-specific weights for mental retardation for 0-4 year olds for untreated (dw=0.469) and treated (dw=0.394) cases.

Table 7 shows the estimated aggregate disability weights for each disease state using the GBD 2010 and GBD 1990 disability weights for each individual manifestation. We see considerable variability in the disability weights. Although the results using GBD 2010 weigh may become more widely comparable to other future disability weight estimates, the GBD 1990 weights include consideration of age-specific and treatment-specific factors. For further comparison, Table 7 includes the results of the only one prior study that evaluated the impact of CRS on population health using QALYs (i.e., a metric essentially equivalent to DALYs for DALYs estimated without age-weighting).[113] This study performed a cost-utility analysis based on the incidence of defects among 11 cases of CRS born after a rubella outbreak in the Netherlands in 2004-2005 and 2 spontaneous abortions, and used disability weights derived from surveys of health care professionals in the Netherlands. Table 7 compares to the incidence of defects and disability weights from our analysis (based on 115 pooled cases) to the 11 CRS cases (i.e., omitting spontaneous abortions not considered here). Proportionately, the Dutch study reported approximately twice as many cardiac and central nervous system (CNS) defects, no eye defects, similar hearing impairment, and a majority of intellectual disabilities occurring in combination with hearing and cardiac defects. The Dutch study used disability weights much more like the GBD 1990 weights, which reflects decreases in the GBD weights
that occurred with the 2010 estimates relative to GBD 1990 and assessments from Dutch medical panels used to derive the Dutch estimates. Assuming optimal treatment provided to 0%, 25%, 75%, and 100% of cases in low-, lower middle-, upper middle-, and high-income countries, respectively, we estimated 29 to 26 undiscounted DALYs per CRS case for low- to high-income countries using GBD 2010 weighting and approximately 39 DALYs per CRS case using GBD 1990 disability weights. Given the higher disability weights of GBD 1990, the DALYS per case for high income countries with low mortality and thus more infants surviving with severe disability becomes similar to the DALYs per case for low income countries, in which high mortality occurs and the infants that survive live for fewer years with severe disability.

Discussion

CRS leads to significant disability with a wide spectrum of potential clinical presentations. Most of the available data on CRS outcomes come from developed countries in which infants generally benefit from surgical intervention for cardiac and eye defects and they receive life-long supportive care for hearing and intellectual disabilities. Similar treatment may not occur in developing countries in which CRS poses the greatest risk to population disease burden given the lack of immunization. We estimated DALYs for CRS that included assumptions about relative levels of treatment associated with different income levels to demonstrate the significantly higher disability per CRS case that occurs without treatment, which in our analysis depends on income level.

Our analysis does not quantify the significant costs associated with delivering treatments, although treating manifestations of CRS to improve survival and the quality of life requires substantial resources (e.g., surgical intervention and/or long-term specialized care). Our results demonstrate the significant improvement in survival associated with the treatment of cardiac defects and the reduced burden of long-term disability in the context of much lower DALY estimates for CRS cases in high income countries than in low income countries, despite a longer life expectancy in high income countries (i.e., even with more years of life lived with disability). We expect relatively low economic productivity achieved by some CRS cases, because even with appropriate amplification and training, severe deafness can impair speech and comprehension.[70] Our DALY estimates do not capture the increased burden on caregivers responsible for infants and children with CRS, which in some countries may impact overall productivity in the family (i.e., require that one adult who would otherwise work outside the home stay home to care for the family member with CRS). Future studies will need to characterize the costs associated with treatment to support economic analyses that consider the full benefits and costs of rubella vaccination.

We highlight several limitations of our review and analysis. First, we found many terms poorly defined or used differently across studies, which limited our ability to consistently interpret the evidence and our efforts to standardize the outcomes data. Although two authors coded all studies for purposes of our analysis, we recognize the original authors conducted their studies to meet their objectives and others may offer different interpretations of the evidence. We found the evaluation of the central nervous system (CNS) manifestations the most challenging aspect of CRS to interpret. Twenty studies reported a broad range of CNS abnormalities other than intellectual disability, most commonly cerebral palsy, convulsions, spasticity, and seizures. We could not discern the conclusiveness of the diagnoses or compare them across studies. We compensated for this by assuming relatively higher severity for the CNS outcomes that we included. The association between intellectual disability and dual hearing and eye defects may reflect greater severity of combined effects, or it could relate to information bias that might arise if testing and diagnosis of intellectual disability occurs more frequently in children treated for
hearing and/or visual impairment. We also used deterministic methods to map comorbidity frequency and severity to the health states rather than conducting microsimulations as done in the GBD 2010.[114] We noted significant differences between the GBD 2010 and GBD 1990 disability weights, which led to a relatively large difference in the estimated DALYs lost per CRS case. Comparisons of burden of disease studies highlight the challenges associated with variability and uncertain associated with disability weight choices.[115] Following the release of the GBD 2010, some experts raised concern about the significant decrease in the disability weight for blindness (i.e., 0.60 to 0.19) between the GBD 2010 and GBD 1990.[116] Studies also review the challenges associated characterizing disability weights (i.e., health utilities) for childhood health states,[117] which reflect inadequate health state classification instruments that consider the dynamics of child development or apply to children under 5 years old, and the reliance of using proxies (e.g., parents) for measuring and valuing child health.[118]

As generalized measures of health based on the opinions of a largely healthy population about disease states they have likely not experienced, disability weights, and consequently disability-adjusted life years, are subject to a number of biases. Societal values about the importance of retaining certain biological functions or shame associated with specific disease states may disproportionately represent some diseases as more severe than the experience of individuals in that disease state. For example, blindness could appear more severe to non-affected individuals than other sensory losses such as deafness due to more obvious outward manifestations of blindness during daily life compared to deafness. While the descriptions of disease states attempted to be accurate, respondents would have an imperfect impression of the daily activities affected by a disease they have not experienced. Applying a single average opinion of the magnitude of morbidity of a disease state, such as blindness, to every individual predicted to be affected by that disability across all strata of society also discounts the importance of mediators of that experience. For example, blind individuals from a more advantaged social network maybe able to benefit significantly from appropriate schooling and social support, while cases from a disadvantaged group could be further disadvantaged from denied opportunities.

Critical gaps remain with respect to the global burden of CRS and its health and economic implications. The lack of studies in developing countries underscores the importance of performing additional studies that characterize the impacts of CRS in these areas and provide better information about the impact of treatment on outcomes. We hope that this analysis will motivate future studies, particularly in less developed countries, to collect additional data. In addition, we found very limited information about the longitudinal impacts of CRS, which led us to make assumptions about mortality reductions based on highly limited evidence. We suggest that the authors of the studies reviewed here might provide very useful information by revisiting the outcomes for their cohorts to improve the estimates of the proportions of cases with different outcomes and to better characterize survival. As countries increasingly introduce rubella vaccine, we suggest the need for enhanced surveillance and active investigation to assess the impact of rubella vaccine on population health.

We hope that this review and our development of a DALY for rubella will encourage more consideration of national and global health and economic costs of rubella and CRS. By providing DALY estimates, we expect that policy makers will now more fully consider the significant disability associated with CRS in the context of their rubella immunization decisions.

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References


Table 1: Limitations affecting quality of evidence, weights (0=no adverse effect on study quality, 3= critical limitation), and the count of the 66 study populations for which we observed the limitations

<table>
<thead>
<tr>
<th>Study characteristic</th>
<th>Weight</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design and methods</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rubella infection in pregnancy data collection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. ≥50% prospective</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>2. &gt;50% retrospective</td>
<td>1</td>
<td>59</td>
</tr>
<tr>
<td>Infant outcomes data collection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Only prospective</td>
<td>0</td>
<td>25</td>
</tr>
<tr>
<td>4. Prospective and retrospective</td>
<td>1</td>
<td>16</td>
</tr>
<tr>
<td>5. Only retrospective</td>
<td>2</td>
<td>25</td>
</tr>
<tr>
<td>Physical exam</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. No major limitations (cases examined multiple times during infancy and early childhood)</td>
<td>0</td>
<td>30</td>
</tr>
<tr>
<td>7. Majority of cases examined exclusively within the first 2 years of life (missed outcomes typically detected after age 2 year)</td>
<td>1</td>
<td>19</td>
</tr>
<tr>
<td>8. Majority of cases examined exclusively after 2 years of age (missed early outcomes, including early deaths and defects)</td>
<td>1</td>
<td>17</td>
</tr>
<tr>
<td>9. Physical exam not described</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>10. Physical findings derived from chart review, survey, or surveillance reports</td>
<td>3</td>
<td>18</td>
</tr>
<tr>
<td><strong>Quality of outcomes data</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. No major limitations</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>2. Intellectual disability not clearly defined or fully represented</td>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td>3. Unspecified or inadequate lab confirmation for &gt;50% of cases</td>
<td>2</td>
<td>28</td>
</tr>
<tr>
<td>4. Major data inconsistencies within publication or serial publications</td>
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<td>20</td>
</tr>
<tr>
<td>5. Case definition not specified or includes non-specific symptoms</td>
<td>3</td>
<td>32</td>
</tr>
<tr>
<td><strong>Directness of reported outcomes to desired measure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. No major limitations</td>
<td>0</td>
<td>25</td>
</tr>
<tr>
<td>2. Timing of maternal exposure or infection not specified</td>
<td>1</td>
<td>34</td>
</tr>
<tr>
<td>3. Children recruited from specific disabled population (biased sample)*</td>
<td>3</td>
<td>22</td>
</tr>
<tr>
<td><strong>Consistency of outcome effects across studies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. No major limitations</td>
<td>0</td>
<td>59</td>
</tr>
<tr>
<td>2. One major defect (hearing, cardiac, or eye) not confirmed or reported*</td>
<td>3</td>
<td>7</td>
</tr>
</tbody>
</table>

*Limitations that preclude quantitative evaluation of study.