

## Research Article

# Congenital Rubella Elimination on Southern Italy: Elimination Delay

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## Abstract

**Background:** Feasibility of congenital rubella syndrome (CRS) elimination has demonstrated on Americas. In line with WHO Europe commitment, in Italy, a two dose schedule and 1- time catch-up campaign on primary school student had launched, on 2003, and surveillance on CRS, on 2005. Starting 1997, Regional Health Agency of Campania (ASSRC- OER) implemented a surveillance system, including one referring clinical center (PIRC) for care, reporting and training, and a delivery hospital network.

**Objectives:** On the period 1997-2015, secular CRS trends analysis according to MMR coverage, postnatal rubella report and birthrate.

**Method:** Systematic congenital rubella infection (CR) risk assessment on newborn and suspected infant referral to PIRC for case diagnosis and management. Trends and outcomes reporting to ASSRC-OER. Performances evaluated on repeated capture-recapture activities on hospital discharge registry.

**Result:** On overall 296 referrals considered eligible, 261 (88%) completed diagnostic assessment. CR and CRS diagnosis were confirmed on 63 (24%) and 45 (17%) infant, respectively. Twenty-eight CRS cases were diagnosed on referral whose mother reported epidemiological linkage and/ or findings on gestation. Overall definite CR and CRS annual mean incidence were 5.44 and 3.89 out of 100,000 live newborn. Persistence of cyclical epidemic clusters and differences between the period preceding and following two dose schedule and 1-time catch up campaign, and case surveillance implementation were shown [3.8 and 7.8 out of 100,000 live newborn, respectively]. The overall number of postnatal rubella infection reports decreased by time. During CR infection epidemics, report number increased sharply before and a little after the catch up campaign and national surveillance start up. First dose MMR coverage sharply increased up to 2005, stagnated <90% up to 2012, and slightly decreased, thereafter.

**Conclusion:** In Campania, CR infection and CRS incidences are still exceeding WHO threshold fixed for control, depending on insufficient measles vaccine coverage at rubella routine vaccination starts up, stagnating first dose MMR coverage, missing supplementary activities targeting young adults, and poor medical training.

## Keywords

- Rubella
- Congenital
- Epidemiology
- Surveillance
- Elimination

## ABBREVIATIONS

CR: Congenital Rubella; CRS: Congenital Rubella Syndrome; CRS-Exp: Expanded Rubella Syndrome; CRI: Congenital Rubella Infection; MMR: Measles-Mumps-Rubella Vaccine; ASSRC-OER: Campania Region Health Agency; PIRC: Perinatal Infection Regional Center and Congenital Rubella Cohort on Campania Region; NPMCRE: National Plan for Measles and Congenital Rubella Elimination; RePuNaRC: Network of Delivery Centre Neonatologists on Campania Region; SIA: Supplementary Immunization Activity

## INTRODUCTION

Rubella is usually a mild self-limited often undiagnosed or misdiagnosed infection. Its impact depends on teratogen effect, particularly when maternal infection is acquired just before or

early in pregnancy [namely, congenital rubella syndrome CRS [1]. Without a surveillance strategy, infants affected by moderate or severe CRS are readily recognizable at birth, whereas mild and asymptomatic congenital rubella CR infection might remain undetected at birth and even for life. Two-dose childhood universal vaccination schedule with periodic Supplementary Immunization Activity SIA on young adult has already beaten CRS in the Americas. It remains on WHO European region, particularly in Poland, Italy and Romania [2].

In Europe, WHO Regional Committee adopted CRS control goal <1/100,000 live births, starting 2005 [3]. As objectives were not achieved on 2010, commitment has renewed and elimination postponed to 2015, and then to 2020 [4,5]. Member States high quality surveillance has recommended ensuring sporadic cases detection.

In Italy, 1-dose monovalent measles vaccine schedule was replaced by 1-dose MMR schedule for 15 months old children, on early 1990s, and included in the national immunization program, since 1999 [6]. Starting 1972 ending 2004, monovalent rubella vaccine for susceptible girl was available; furthermore, coverage data are missing. Starting 1988 ending 1991, a window for CRS reporting showed CRS persistence with typical pattern [7]. On November 2003, National Plan for Measles and Congenital Rubella Elimination NPMCRE introduced 2 doses MMR vaccine schedule and promoted 1-time SIA targeting primary school students born 1991 to 1997 [7]. Opportunities for MMR offer to adolescents and young adults women, including post-partum vaccination of susceptible mother, were listed but not facilitated by medical staff training and commitment, and public awareness campaign for the population. First dose coverage was annually reported to Health Ministry, but depending on missing national immunization register, second dose and catch-up campaign coverage remained unmonitored. On 2005, to monitor progress congenital and gestational rubella reporting became mandatory for clinicians [8]. On 2011, as objectives have failed, elimination goal has postponed to 2015 [9].

Campania region is a geo-political district of southern Italy with 5,833,332 inhabitant 9,6% of national population. Live births on the study period ranged between 69,651 and 50,907 Mean 60876,6 [10]. Mean age at first delivery was 30, range 29-31; over 90% of the pregnant women receive public care, including outer-born and not resident population. At MMR vaccine universal implementation, local measles vaccine coverage was 65%. On 2001, thousands of cases with 4 deaths and a shift of incidence toward older age groups were reported [11]. The same shift was registered on rubella report to Health Ministry system [7].

Starting January 1997, as depending on low MMR coverage CR burden was expected, ASSRC-OER implemented a reference center PIRC for CR case investigation and management, and trends and outcomes monitoring [6]. Starting 1998, a delivery hospital neonatologist network RePuNaRC supported PIRC activities [12]. After national surveillance implementation, due case format for national reporting were timely sent to responsible authority.

Secular trends on CRS and CRI incidence according to first dose MMR vaccine coverage, postnatal rubella case report number in the central database at the Health Ministry and annual live births number were assessed to inform strategy.

## MATERIALS AND METHODS

### Recruitment

PIRC activities represent an area-based open cohort study involving ASSRC-OER, RePuNaRC including 67 delivery centers and covering >89% of local birthrate, and PIRC. RePuNaRC acts as a sentinel unit, by systematically evaluating CR infection risk on live newborn based on reports, clinical findings and epidemiological link on gestation, and CRS findings presence at birth. Babies with findings and/or confirmed, probable or only possible diagnosis of rubella on gestation in the mother, were centrally referred [13,14]. PIRC supported online RePuNaRC activities, warranted initial training and periodic refreshment on rubella infection and CR, feedbacks, rigorous case investigation

and laboratory confirmation, and ASSRC-OER yearly reporting on trends and outcomes. Upon PIRC enrolment, mothers-child dyad diagnosis precision was re-evaluated.

### Diagnostic evaluation

Diagnostic investigation included specific IgM and IgG testing at time 0, 4, 6 and 9 to 12 age months, expert cardiologist, audiologist, neurologist and ophthalmologist examination, AABR, EEG and neuroimaging at enrollment. Re-evaluation was carried out on four months aged infected patient and as needed, thereafter [14]. CR diagnosis has confirmed or rule out based on presence or absence of specific IgM within age 3 months, persistence or disappearance of rubella-IgG beyond age 6 months, and low rubella IgG-avidity in cases with IgG persistence, respectively. CRI was diagnosed based on serological confirmation without systemic and/or end-organ findings, namely eye, heart, hearing and brain. CRS was diagnosed based on the presence of at least one A or  $\geq 2$  B findings where category A conditions include cataract, congenital glaucoma, congenital heart disease, loss of hearing and pigmentary retinopathy and those in category B include purpura, splenomegaly, microcephaly, developmental delay, meningoencephalitis, radiolucent bone disease, jaundice that begins within 24 hours after birth [13,14]. Congenital expanded rubella syndrome CRS-exp was diagnosed on CRS cases with systemic disease.

### PIRC performance analysis

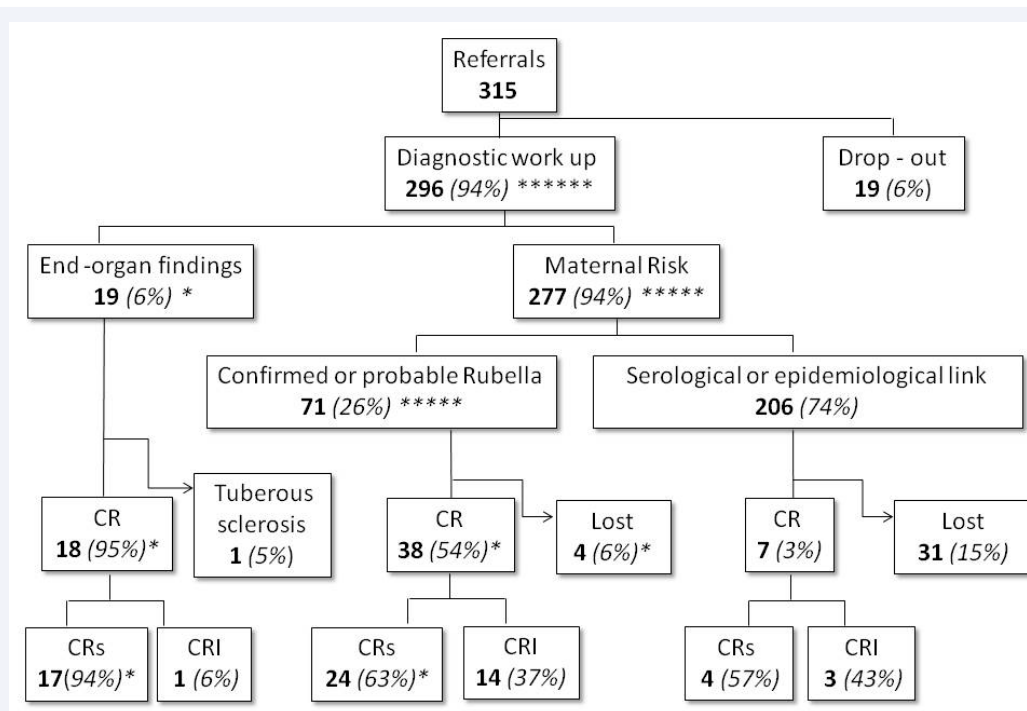
On the period 1997- 2002, reporting reliability was assessed on a capture-recapture study [12]. Briefly, regional hospital discharge registry had scanned to identify hospitalizations for CRS codes, individual records were retrieved and diagnosis revisited with interview of the hospital mother and child case managers, and the family pediatrician. Further five confirmed CRS cases were detected and included on cohort study, after parental informed consent. On 2015, a new capture-recapture activity on the regional hospital discharge registry, including 2006 to 2013 period, displayed no additional case for CRS codes.

### Analysis

Statistical analysis was performed using Epi Info software version 7. Categorical variables were summarized using frequencies and proportions and continuous variables as median and range. Exposure risk has calculated as Odds ratio. Statistical significance was attributed to a p value of < 0.05.

## RESULTS AND DISCUSSION

Starting January 1, 1997 ending December 31, 2015, on overall 315 referrals, 296 94% , delivered from 290 mothers, were considered eligible to diagnosis and 261 88% completed diagnostic assessment Figure 1. Nineteen infant 6% have withdrawn according to negative confirmatory test on the mother positive IgM and negative or border-line stable IgG or high IgG avidity early on gestation and lack of epidemiologic link on gestation. Thirty-five 15% infant were lost, all of them on the subgroup with negative rubella IgM and without clinical findings at delivery hospital first examination, and thus presumably not infected. Confirmed CR infection was diagnosed on 63 out of 261 24% patients, including 33 CRS 52%, 12 expanded CRS 19%



**Figure 1** Diagnostic Outcomes on Infant Referred for Suspected Congenital Rubella Infection (PIRC Cohort, Campania Region of Italy, 1997- 2015) Legend: \*twin pair; End organ findings: heart and/or eye defect and/or hearing loss and/or central nervous system functional findings and/or neuroimaging abnormalities. CR congenital rubella infection, CRS Congenital Rubella Syndrome, CRI laboratory confirmed congenital rubella infection without end organ findings [12,13].

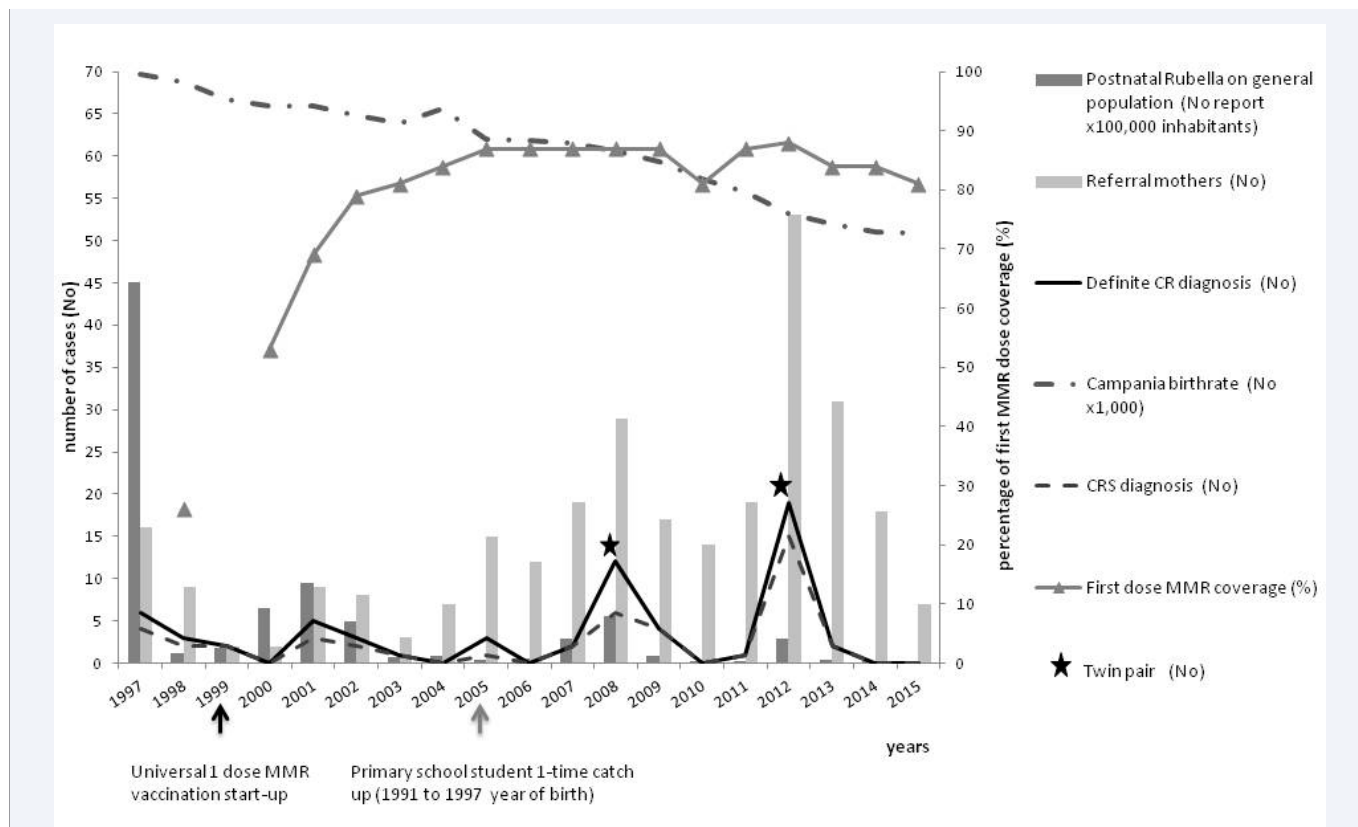
and 18 CRI 29%, respectively [13,14]. Noteworthy, one genetic disorder with CRS overlapping findings and negative rubella IgM test was diagnosed among referrals with end-organ findings 5%, and 28 CRS 10% on referrals with negative clinical examination at birth and epidemiologic linkage on gestational history [24 63% on confirmed or probable maternal rubella on gestation group and 4 57% on maternal positive rubella IgM and IgG or epidemiologic link group, respectively]. On 17 38% definite CRS diagnosis, the mother remained unaware of the risk until delivery because of missing suspicion [4 cases 9% with epidemiologic link, and 13 29% with misdiagnosed acute rash]. Two CRS cases occurred on twin couples one stillbirth.

On the period January 1, 2005 to December 31, 2013, according to surveillance data analysis displaying a national annual mean incidence of 1.5/100,000 live births, CR was shown still an issue in Italy [15]. Unfortunately, the incidence seems underestimated according to the followings: 1. Report were sent by 11 out of 21 regions; 2. Overall, 38 out of 75 51% confirmed cases and almost all cases registered on 2012 epidemics were reported in Campania where surveillance is reinforced; 3. Overall, 43 definite CR diagnosis instead of 38 were registered on PIRC cohort, including 31 CRS, thus suggesting data flow mismatching; 4. On a retrospective case-finding study performed in Puglia, a region with high first dose MMR coverage 93% and no CR case report from 2001 to 2012, one CRS, two confirmed and four suspected CRI cases were detected on the period 2003-2011 by a capture-recapture approach on hospital discharge database [16]. Good subnational data might inspire a policy entrusting regional clinical centers on CR care and surveillance.

In Campania, overall definite CR and CRS annual mean incidence were 5.44 and 3.89 out of 100,000 live newborn, thus widely exceeding the WHO threshold fixed for CRS control.

As shown on Figure 2, rubella cyclical pattern persists in Campania and epidemic CR and CRS clusters, progressively increasing in size, were registered on 1997, 2001-2002, 2007-2009 and 2012 6, 8, 18 and 19, and 4, 5, 12 and 15 cases, respectively. Differences were shown between the period A preceding 1997 to 2005 and B following 2006 to 2014 two dose MMR schedule, 1- time catch up campaign and case surveillance implementation. CR mean incidences were 3.8 and 7.8 out of 100,000 live newborn on period A and B, respectively OR 2.16, 95% CI 1.28- 3.62; p 0.004. CRS mean incidences were 2.52 and 5.85 out of 100,000 live newborn on period A and B OR 2.31, 95% CI 1.24 to 4.3; p <0,0001, respectively. Overall, mother-child referrals increased by time with differences according to A and B periods OR 3.45, 95% CI 2.64- 4.53; p<0,001. On general population, overall rubella infection report number No 4812 declined by time. During CR epidemics 1997, 2001 report number increased sharply whereas on 2008 and 2012 epidemics increased suddenly but a little OR 5.49, 95% CI 4,56-6,62; p< 0.0001 [17,18]. First dose MMR coverage sharply increased up to 2005, stagnated around 80% to 88% up to 2012, and decreased slightly from year to year, thereafter in line with general decrease on attitude to immunization [6,19]. Birthrate declined by time.

New national laws are introducing mandatory 2 dose MMR vaccination of 1-16 old scholar citizens and unaccompanied foreign minors, and of school, health and social staff [20]. As a consequence, an increase on herd immunity is expected on



**Figure 2** Secular Trends on Definite Congenital Rubella (n = 63), Congenital Rubella Syndrome (n = 45 cases), and Referrals (n = 290), Postnatal Rubella Reports on General Population (Number 4812), MMR Coverage Percentage, and Birthrate (PIRC Cohort, Campania Region of Italy, 1997-2015). First dose MMR percentage for 2013 was missing on database at Health Ministry and kindly supplied by OER- ASSRC as provisional, due to the ongoing implementation of a web-based surveillance system for infectious diseases on Italy. Legend: infant with definite diagnosis of congenital rubella (CR); infant with definite diagnosis of congenital rubella syndrome (CRS).

general population. Furthermore, early positive side-effects on CR incidence are hard to predict because pockets of unprotected reproductive-age adults will not be met, and children vaccinated on 1-time catch up campaign of 2005 are yet younger than national fertility age 20 to 26 years aged versus 32 [10]. According to 2011 WHO position paper, without a speed-up campaign SIA targeting adult young men and women, elimination goal might be achieved only within 10–20 years [21].

## CONCLUSION

In Italy, current passive CR and CRS surveillance system displayed severely undersized whereas the system implemented in Campania region, based on a deep-rooted network of delivery hospital trained neonatologists and a clinical center performing high level diagnosis, performance assessment and active regional health authority reporting, seems a promising strategy for monitoring rubella control achievement.

Our experience and other subnational evidences point-out the need for MMR acceleration activities to achieve the goal of rubella control on a reasonable period of time within 10 years. New national vaccine law making mandatory MMR vaccination of 1-16 years old scholar and of scholar, health and social staffs may increase further the risk of facing rubella infection on gestation at mean local reproductive age. In fact, even women vaccinated in catch-up campaign of 2005 will reach their fertility age by 5

to 11 years. Additional training in rubella and CRS in health care workers, periodic SIAs targeted to young adult men and women, combined with a public awareness campaign to sensitize the population to the dangers of rubella and CRS, and the importance of vaccination might permit the most rapid elimination in Campania. We recommend that public health officials use infectious disease modeling to design a rubella vaccination strategy which will permit the most rapid elimination of rubella.

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