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REVIEW

Strategies for elimination of rubella in pregnancy and of congenital rubella syndrome in high and upper-middle income countries

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Keywords

Rubella • Vaccination • Congenital rubella syndrome • Surveillance • Coverage

Summary

Rubella infection generally leads to mild symptoms; otherwise, in pregnant women it can cause severe damages. The only way to prevent rubella is vaccine. Before the introduction of the vaccine, up to 4 babies in 1000 live births were born with CRS.

This work aims to review the most important strategies for the elimination of CRS in upper and high-income countries.

Papers were selected through a PubMed search up to January 2019, using keywords rubella, congenital rubella syndrome and epidemiology. Articles published in the last 12 years and referred to upper income and high-income countries in title or abstract were included.

Sixty-five papers were selected dealing with one or more of the following strategies: increasing of rubella vaccination coverage in childbearing age women, males, immigrants; exploitation of all appropriate occasions; improving of rubella surveillance.

Despite numerous suggestions and indications for valid strategies to eliminate rubella in pregnancy and congenital rubella syndrome, a practical application is often missing.

Introduction

Rubella is an acute viral infection that generally leads to mild symptoms, such as fever and rash in children and adults. It spreads by contact with infected nasal or throat secretions or by breathing droplets sprayed into the air when an infected person sneezes, coughs or talks. In pregnant women, however, rubella infection can cause severe damages. During the first trimester, it can result in miscarriage, fetal death, stillbirth, or infants with congenital malformations, known as congenital rubella syndrome (CRS). These children can present eye and heart defects, hearing impairments and other lifelong disabilities as diabetes and thyroid dysfunctions. All these are serious clinical conditions, with high costs in terms of therapy, care and disabilities [1].

The only way to prevent rubella is vaccination; before the introduction of the vaccine, up to 4 babies in 1000 live births were born with CRS [2]. The widely used rubella-containing vaccine (RCV) is safe and effective and one dose is about 97% effective in preventing rubella [1].

Since the 1980s, WHO recommended national use of routine childhood rubella vaccination. Three World Health Organization (WHO) Regions (American, European and Western Pacific Region) have rubella and CRS elimination goals [3]. WHO, summarizing global progress toward rubella and CRS control and elimination, reports that as of December 2016, 152 of 194 countries had introduced RCV into their national immunization schedule. In the WHO European Region 95% of 53 Member countries incorporated a RCV by 2009 into their routine childhood immunization programs, and, in 2010, 67% of the WHO Member States included rubella in association with measles vaccines in their national immunization programs [4-6].

Furthermore, according to WHO's guidelines, a key strategy for achieving rubella elimination is the implementation of a high-quality Surveillance System. Today we can find Surveillance System for rubella, rubella in pregnancy and congenital rubella syndrome in most of the American, European and Western Pacific Region's countries [2].

Unfortunately, despite the existence of well-established immunization programs and the presence of Surveillance Systems, in high and upper-middle income countries epidemiological data show that rubella, rubella in pregnancy and CRS still represent an important Public Health issue.

In this scenery, a review of the existing literature was performed:

- to identify the most important strategies for the elimination of rubella in pregnancy and CRS in high and upper-middle income countries;
- to highlight aspects that can lead to an improvement in the fight against CRS.

Materials and methods

Papers were selected through a PubMed search up to January 2019, using the following keywords: rubella and congenital rubella syndrome and epidemiology.

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Inclusion criteria were (Fig. 1):
- papers published from 2007 to 2018;
- papers referred to high and upper-middle income countries [according to the New country classifications by income level: 2017-2018 by the World Bank (69)] in title or abstract;
- papers with abstract;
- papers in English and other languages of the European Community.

Full text of selected articles was evaluated and papers were excluded if they did not present data about national surveillance systems and strategies to improve vaccination coverage.

The analysis was performed in 65 articles considering three topics:
- strategies to increase coverage in risk groups: women in childbearing age, males not included in universal rubella vaccination programs and immigrants;
- strategies to use every opportunity to offer immunization, like different places or situations;
- strategies to implement surveillance system considering solution for correcting underestimation, collaboration with laboratories and integrating measles and rubella surveillance.

Results

The selected papers addressed at least one of the following strategies for the prevention of rubella in pregnancy and CRS: rubella vaccination coverage in childbearing age women, males and migrants; different opportunities to offer vaccine; problems related to rubella surveillance [1, 4, 6-68].

Coverage

Rubella vaccination coverage was considered in fifty-one (78%) articles (Tab. I).

Rubella vaccination coverage in childbearing age women

Among the twenty-two selected articles that considered this point, many underlined that comprehensive strategies are needed to prevent CRS [8, 9, 25, 31, 51, 55, 66]. High levels of immunity (≥ 95%) in the general population and immunization of susceptible subjects are the cornerstones to prevent CRS [50].

Seroprevalence studies are useful to identify susceptible groups that may require additional prevention strategies and should be carried out periodically [25, 41]. A great number of childbearing age women are still unprotected from rubella [6, 10, 44, 54]. Three studies in women of reproductive age showed that between 14 and 17% were susceptible to rubella [8, 29, 66]. In Greece [8] vaccination coverage was 18.5% while in China [66] generally lower vaccination coverage was indicated. Countries should make efforts to reach women of childbearing age either through routine services or mass campaigns [1, 38]. The priority is to reach a high coverage in susceptible women, offering vaccination in every occasion, in particular to immigrant women [35].

Supplemental immunization activities are required also for countries, that revised their immunization strategies. In fact, when rubella vaccination was offered to all children at 12 months instead of immunizing only girls at 11-13 years of age, for some time the amount of susceptible people increased in general population, and among them we can find women in childbearing age [25].

Catch-up programs are necessary to reach susceptible individuals missed in routine immunization even if vaccine coverage is as high as 97-99% [26] and they have been implemented in many countries [25].

Immunization strategies should be integrated with preconception care [19, 41]. When this is not possible, susceptible women should be vaccinated during the postpartum period [10]. Females of childbearing age and pregnant women must be aware of mother-to-child transmission to reduce the incidence of CRS [14, 46] and a study demonstrated that a high proportion (36%) of the pregnant women of the study group was unaware of the risk posed by rubella infection contracted during pregnancy [29].

Rubella vaccination coverage in males

For many years the prevalent vaccination strategy for rubella has focused on women coverage [32]. In this way the male population has become a major reservoir of susceptible subjects in many cases [42, 58]. Therefore, to interrupt endemic rubella transmission, supplementary immunization activity should be focused on male adults [43, 62]. For example, three countries (Chile, Brazil and Argentina) focused campaign between 1999 and 2006 on women and transmission and outbreaks of rubella mainly occurred among adolescent and adult males [12]. Therefore, the immunization strategy was focused on males starting in 2007. In Brazil it was shown that the greater incidence in men lead to new outbreaks of CRS [39]. In Mexico and Costa Rica no cases of CRS have been recorded since 2008, thanks to a universal vaccination strategy [6, 39].

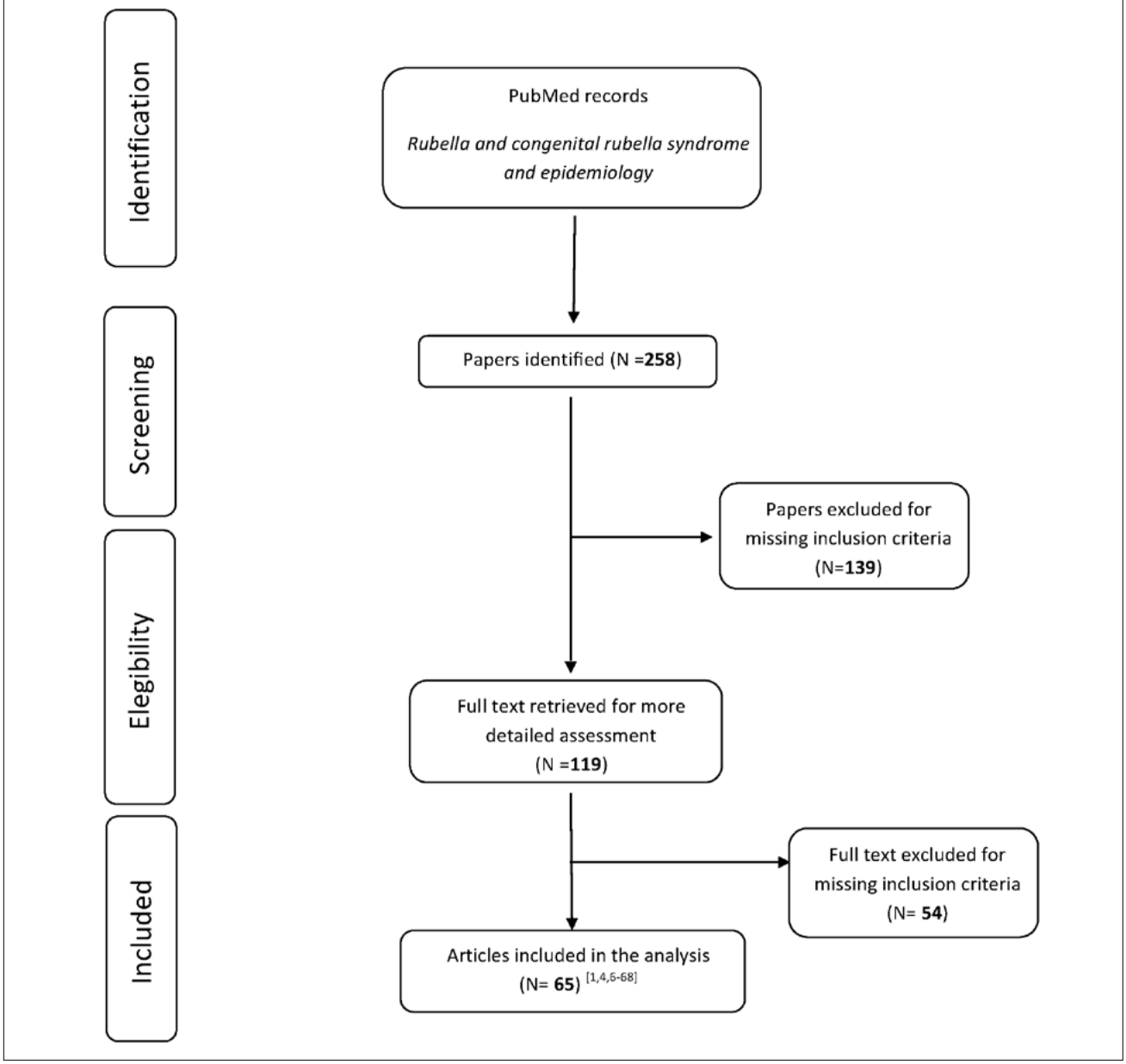
In the American Region, in countries that had vaccinated only women during mass campaigns, outbreaks of rubella occurred in 2007 despite a reduction of 97.8% of confirmed cases [13].

In Europe, many countries introduced rubella vaccine in females earlier than in males. In Catalonia, it was shown that infected males had contact with potentially pregnant females of the same age and therefore males became the target of specific vaccination campaigns [34].

Poland and Romania, as a result of a strategy that initially focused on females, experienced rubella outbreaks that predominantly affected males in 2012 [1]. In Poland, the selective vaccination of adolescent girls since 1989 explains the 81% of cases among 15-29 year-old males during the outbreak in 2013 [41].

In Japan, there has been a large outbreak of rubella in 2012-2013 and most cases were reported in males (aged 20-49 years). The following year Tokyo Metropolitan Government began offering free (or reduced cost) vacci-

Fig. 1. Flow chart for articles selection.



nations to females of childbearing age and their partners as a response to the outbreak [56].

Rubella vaccination coverage in immigrants

Vaccination policies are not common to all countries. In particular, rubella is not a priority for many of the migrants' countries of origin [33] and generally the percentage of seronegativity is higher in foreign born women, especially those from Asia [23]. In a large study performed in Ireland rubella susceptibility was 6% in European mothers and 11.4% in women born outside the European Union [40].

Immigrant women, who presently represent the population with higher fertility [28] and that are one of the most vulnerable and frequently neglected groups, represent a priority for rubella vaccination [7, 10, 32].

Rubella elimination in Europe, may be obtained also through the control of transmission form countries with high incidence [25].

In UK most of the recent cases of CRS have been observed in infants of foreign born mothers because of the lack of vaccination programs or sub-optimal coverage in their countries of origin [59]. Further attention is needed to respect the catch-up program after entering the UK [9]. Other important occasions of transmission can be the visit of relatives and friends from endemic countries [64].

Pregnant women who return to their countries of origin with endemic virus circulation may be on danger (i.e. Nigeria) [63].

Women from countries that do not have specific immunization programs for rubella may give birth to an infant with CRS [19, 68]. For preventing CRS in immigrants,

Tab. I. Strategies for preventing rubella and CRS – Coverage.

References	Authors / Strategies	Coverage		
		Childbearing age women	Males	Immigrant
7	Bonanni 2007			x
8	Giuola 2007	x		
9	Jin 2007	x		x
10	Rota 2007	x		x
12	CDC 2008		x	
13	Weekly epidemiological record 2008		x	
14	Canepa 2009	x		
18	McElroy 2009			x
19	Pandolfi 2009	x		x
23	Hernandez Diaz 2011			x
25	Usonis 2011	x		x
28	Bechini 2012			x
29	Calimeri 2012	x		
31	Metcalf 2012	x		
32	Song 2012		x	x
33	Tkadlecova 2012			x
34	Barrabeig 2013		x	
35	Bechini 2013	x		x
38	Cutts 2013	x		
39	Mongua Rodriguez 2013		x	
40	O'Dwyer 2013			x
41	Paradowska-Stankievicz 2013	x	x	
6	Bouthry 2014	x	x	
42	Grangeot-Keros 2014		x	
43	Yamada 2014	x	x	
44	Khandaker 2014	x		x
45	Lo Giudice 2014			x
46	Morioka 2014	x		
48	Cozza 2015	x		
50	Giambi Filia 2015	x		
51	Jyoti 2015	x		
1	Lambert 2015	x	x	
54	Neu 2015	x		
55	Plans 2015	x		
56	Sugishita 2015		x	
58	Kinoshita 2016		x	
59	Ogundele 2016			x
62	Mori 2017		x	
63	Baltimore 2018	x		x
64	Bukasa 2018			x
66	Meng 2018	x		
68	Seppälä 2018			x

a Canadian study proposes the possibility to offer vaccination to women of childbearing age after investigating their immune status or immediately without serological control [18].

Similarly, an Italian study proposes vaccination of foreign-born women at their first encounter with the healthcare system [35] especially considering that in recent years in Italy there has been an increased number of immigrant women (to joint family members) and also a large number of women employed as care providers or domestic workers [45].

Appropriate occasions

Eighteen of the selected articles (28%) consider this point (Tab. II).

It is important to take advantage of every opportunity of encounter with the health system to inform about risks of CRS and provide an active vaccination offer to susceptible women in childbearing age in different locations and situations [14, 29, 48]. Several strategies have been suggested to increase the achievement of vaccine offer in susceptible:

Tab. II. Strategies for preventing rubella and CRS – Opportunities.

References	Authors / Strategies	Opportunities					
		School and work place	Travel medicine	Post partum post abortion	Vaccination session	First PAP test	Education of clinicians
10	Rota 2007			x			
14	Canepa 2009						x
16	Lugner 2009			x			
22	Gross-Galiano 2011						x
23	Hernandez Diaz 2011			x			
25	Usonis 2011		x				
28	Bechini 2012				x	x	
29	Calimeri 2012			x		x	x
35	Bechini 2013	x		x			
43	Yamada 2014			x			
44	Khandaker 2014	x	x				
48	Cozza 2015		x		x	x	x
50	Giambi Filia 2015			x			
54	Neu 2015			x			
56	Sugishita 2015	x					
57	Vilajeliu 2015			x			
67	Pettinicchio 2018			x			
68	Seppälä 2018			x			x

School and work place

Considering the most appropriate age for vaccination (target age group 10-14), the school may be a privileged place for the promotion [44]. Vaccination of school personnel could also be an opportunity to explore [35]. Mass vaccination is essential to eliminate rubella transmission at workplaces. In a rubella epidemic in March 2013 in Tokyo, the workplace was the most frequent location of transmission, among adults. The Tokyo Metropolitan Government provided financial support for adult MR vaccination to local administrations for 1 year [56].

Visit at the travel medicine service

Vaccination of susceptible people visiting foreign countries could be an opportunity [25, 48]. Susceptible pregnant women should evaluate the danger of travelling to countries where rubella is endemic [44].

Post-partum [10, 16, 23, 54, 68] and post abortion vaccination of susceptible women [29, 35, 67]

It is an opportunity to increase vaccination coverage against rubella and other vaccine-preventable diseases and strategy to protect women and consequently prevent CRS [57].

An Italian research showed 16% of susceptibility to rubella in a two-year period (2014-15) among women accessing voluntary termination of pregnancy in Rome. Among them, only 15% accepted the vaccine [67].

In the Italian national elimination plan, several strategies have been proposed for post-partum vaccination. Vaccination of the susceptible women could be performed before discharge from the ward [29, 50]; or the public vaccination service could take care of the active call and immunization; or the first access of the newborn to the vaccination service could be exploited to vaccinate also the susceptible mother [50].

Many hospitals offer rubella immunization to women not immune for rubella and this strategy was generally shown to be effective. However, a poor adherence to the second dose has been reported [35, 50, 57].

A Japanese study has shown that despite knowledge of the risk of contracting rubella in pregnancy, women do not get vaccinated. Japanese guidelines recommended to investigate the immune status of women during pregnancy and to vaccinate those with low titer in postpartum [43].

Other occasions

It is important however to be able to exploit any access to the vaccination services. In Italy, for example, some studies propose to exploit the opportunity of HPV immunization session or the routine anti-tetanus–diphtheria–pertussis booster dose [28, 48].

In addition, the occasion of the screening tests can be exploited like the first pap-test screening visit at 25 years [28, 29, 48].

In addition is always crucial to improve awareness of clinicians and of healthcare workers because of the role played by general practitioners, health personnel and specialists involved in women's health [14, 22, 29, 68].

Surveillance

Fifty-three of the selected articles (81%) consider this point (Tab. III).

The problem of underestimation

Despite the awareness about the importance of notification in a high-quality Surveillance System, there is a

Tab. III. Strategies for preventing rubella and CRS – Surveillance.

References	Authors / Strategies	Surveillance		
		Underestimation of R and CRS	Laboratories' role	Integrating MR
9	Jin 2007		x	
11	Carnicer-Pont 2008	x		
12	CDC 2008	x		x
13	Weekly epidemiological record 2008		x	x
14	Canepa 2009		x	
15	Forsey 2009	x		
17	Martin 2009			x
19	Pandolfi 2009	x		
20	Bisbo de Filippis 2011		x	x
21	Castillo-Solorzano 2011		x	x
24	Rota 2011		x	
25	Usonis 2011	x	x	
26	Zimmerman 2011	x	x	x
27	Zimmerman Muscat 2011	x	x	x
28	Bechini 2012			x
30	Goodson 2012		x	
34	Barrabeig 2013	x	x	
35	Bechini 2013	x	x	
36	Buffolano 2013	x		
37	CDC 2013	x		x
41	Paradowska-Stankievicz 2013		x	
6	Bouthry 2014		x	x
44	Khandaker 2014			x
47	Chan 2015		x	
49	Giambi 2015	x	x	
50	Giambi Filia 2015	x	x	
52	Martinez-Quintana 2015	x	x	
53	Masa Calles 2015	x	x	
54	Neu 2015			x
55	Plans 2015			x
56	Sugishita 2015	x	x	
60	Paradowska-Stankievicz 2016		x	
61	Vynnycky 2016	x		
4	Grant 2017		x	
65	Edirisuriya 2018		x	
68	Seppälä 2018	x	x	

problem of rubella underestimation due to the variable clinical pattern and to an incomplete reporting, especially in the private sector [11]. Some documents deal especially with the fundamental importance of harmonizing the notification by using standard documents for reporting, introducing the zero-reporting and guaranteeing the notification from regional to central level [49, 50, 53, 56].

CRS is typically underestimated [61], not only because of the lack of notifications. In fact, cases of CRS may go under-recognized due to the asymptomatic nature of rubella infection in mothers and a late onset of CRS symptoms in infants and children [25].

Even if CRS is often a severe disease with specific symptoms (Gregg's triad) [15], it may present with other manifestations like thrombocytopenic purpura, encephalitis [56]. Rubella infection during pregnancy may be asymptomatic or can cause abortion [19].

WHO proposes retrospective search into hospital records as a complementary approach to the surveillance of congenital rubella. However, in most countries only the codes referring to the most severe types of congenital rubella syndrome are considered (deafness, cataracts, heart defects) while the milder, asymptomatic and late-onset cases go unnoticed [11]. In many cases even abortions, stillbirths and fetal deaths are neglected [49, 50].

For this reason, it is mandatory to involve pediatricians, obstetricians, cardiologists, ophthalmologists and otolaryngologists in the surveillance [36], with the recommendation to investigate all pregnant women with fever and rash [37], to follow and record the pregnancy outcomes [52] and to report all the suspected cases of CRS [53]. It is also important the retrospec-

tive search into hospital records, using a wide range of codes [34, 35, 68], so that even the most atypical cases of CRS can be recognized [26, 27].

Strengthening laboratories' capacity

In a high-quality Surveillance System, laboratory role is fundamental, not only for the diagnosis and for the confirmation of the etiology [41, 52]. In fact, laboratory investigations can give information about: susceptibility in pregnant women [26] or women in childbearing age [49]; seroprevalence in the population and in risk groups [50]; success or failure of vaccine [34]; origin of infection through virus genotyping [6, 20, 21, 27].
Worldwide, thanks to molecular biology, surveillance has improved, and the number of rubella virus genotype sequences increased in the last fifteen years [4].
Despite the WHO recommendations and the existence of national reference laboratories, genotyping of the virus is still underused and needs to be increased in most of the member countries [24]. For strengthening CRS surveillance systems it is very important to improve the laboratory confirmation [9, 13, 14, 30, 35, 41, 47, 53, 68], that is often not adequate [25, 60]. Even in Japan where there is a good Surveillance System, not all rubella cases are laboratory confirmed [56].
Investigation concerning levels of rubella specific IgG seropositivity can provide evidence of increase or decrease over the years, giving an idea of how the country proceeds towards elimination [65].

Integrating measles and rubella surveillance

According to different authors [6, 12, 13, 17, 21, 28, 44, 54, 55] and CDC (Centers for Disease Control and Prevention), surveillance for rubella infection benefits from integration with measles surveillance system [37]. In fact, the two diseases may be similar from a clinical point of view, and since the diagnosis is made by using the same laboratory testing methodology, and the vaccination is made by combined vaccines, WHO strongly recommended the integration of measles and rubella surveillance [26, 27].
Measles and rubella integrated surveillance system started in 1999 and took origin from the surveillance system developed for measles. Patients suspected of having measles or rubella infection were searched at the same time for both measles and rubella IgM. PAHO (Pan American Health Organization) has recommended since 1996, that all suspected IgM negative measles cases should be tested for rubella IgM [20].

Discussion

High vaccination coverage and Surveillance Systems are the cornerstones for eliminating rubella and congenital rubella syndrome (CRS).
The increase of rubella vaccination coverage is the target of many published studies. However, in the literature few practical experiences are described and few results of their implementation are presented. The few available experimental studies show that women of childbearing age present obstacles in accepting vaccinations even if they are the most important target [70]. Furthermore, seroepidemiological studies and Surveillance Systems' data from high and upper-middle income countries suggest that many women do not know their immune status regarding rubella [14, 29, 43, 44, 48, 50, 56, 67, 71].
In most situations, a combined rubella and measles vaccine (at least) is currently being used. This is at the same time an advantage because it takes the appropriate opportunities for both vaccines but a disadvantage for rubella that ends up bringing all the fears evoked by anti-measles vaccination.
There are other aspects to be considered, like the problem of the second dose. However, this second dose does not seem to be essential for the prevention of rubella.
It has been shown by mathematical models that a coverage of about 80% is enough to obtain the elimination of rubella. A proportion of 80% is needed in all target groups and there is still a part of the population that is not immunized even in countries with high coverage. At present susceptible groups include women of childbearing age, males not included in universal rubella vaccination programs and immigrants.
In the main risk group of women of childbearing age, we found out two main problems: susceptibility and a low level of awareness. We could face them with adequate health promotion campaigns. Furthermore, it is extremely important to use all the possible occasions to inform about the risk of contracting rubella during pregnancy, to investigate immune status and to actively offer vaccination against rubella. These occasions could be: preconception care, post-partum or post-abortion period, children's routine immunization sessions, adolescent HPV immunization session, the first pap-test screening visit and the routine anti tetanus-diphtheria-pertussis booster dose.
For many years, the prevalent vaccination strategies for rubella have focused only on women coverage, turning men into a reservoir of susceptible subjects and, then, hindering elimination of rubella. For this reason, it is crucial to reach these susceptible males with a supplementary immunization campaign focused on male adults.
Though a recent study estimates that approximately 131,000 CRS deaths in low-income countries may be prevented by increasing vaccination coverage [72], not all countries in the World have vaccination policies and unfortunately, even if they have them, rubella is not considered a priority. Consequently, immigrants and particularly immigrant women represent an important vulnerable group, which increase the risk of transmission of rubella even in those countries that achieved the elimination goal. It is essential to increase coverage among immigrants, through focused vaccination campaigns and by taking advantage of the first encounter with the healthcare system to verify the immune status and to offer vaccination to those who are susceptible [73].
Some more results were obtained on Surveillance Systems. During 2000-2016, there has been an increase of

more than 40% in countries reporting rubella and CRS cases worldwide. Furthermore, in the Region of the Americas and in 33 of 53 countries of the European Region, the elimination of rubella has been reached since 2015 and 2016, respectively [4].

Though these data show a decrease in the number of cases, the limits highlighted in Surveillance Systems are several. To achieve the goal of rubella and congenital rubella syndrome elimination, the existence of an effective and high-quality Surveillance System is crucial [7, 14, 25, 57, 71, 74]. A Surveillance System is currently active in most of the countries in the World and, particularly, in the European Region [50, 53, 75]. But, according to data from CDC, WHO and different authors [27, 48], many of these Surveillance Systems *"do not meet the standard surveillance performance indicators recommended for monitoring progress towards and verification of [...] rubella elimination"* [76], leading to a serious problem of underreporting and, consequently, underestimation [77].

The underestimation of rubella, rubella in pregnancy and particularly of CRS is not only due to the lack of notifications. In fact, cases may go under-recognized because of the wide range of clinical manifestations of CRS and the asymptomatic nature of rubella infection in adults. The solution for this problem could be the education of all healthcare workers, in order to investigate all pregnant women with fever and rash, following and recording the pregnancy outcomes [14, 22, 29, 48]. Moreover, it could be helpful a retrospective search into hospital records using a wide range of codes, so that even the most atypical cases of CRS could be recognized. Furthermore, from a clinical point of view, rubella can be confused with measles. For this reason, WHO recommends the integration of measles and rubella surveillance.

Obviously, it is desirable to overcome the differences among the Surveillance Systems. Although they have been shaped on identical guidelines, the countries' Surveillance Systems are different in some aspects [28]. First of all, "*rubella surveillance across Europe is complicated by the different methods used to collect data in each country [...]*" [25]. The most important difference concerns the case definition of congenital rubella: only in some countries the asymptomatic congenital infection fits in the definition of congenital rubella and, therefore, is reported [11]. Furthermore, not all countries collect information about the origin (autochthonous or imported) of the cases [49]. These differences create difficulties in comparing the situation among countries, and therefore in interpreting the progress in the elimination process.

Possible solutions to all these problems are the standardization of Surveillance Systems, following WHO guidelines. Is mandatory to strength laboratories' capacity, to create a Surveillance System in those countries which still do not have it [27, 78] and to improve the existing ones in all countries across Europe and the World [30, 39, 49].

In conclusion, in addition to the possible strategies (routine childhood vaccination programs, mass rubella immunization campaigns, surveillance of childbearing age susceptible women, surveillance of imported cases, rapid response to outbreaks [38], strengthening of CRS surveillance [17, 19], improvement of laboratory test results) other measures could improve the results and might help elimination efforts. For example: simplified handling and simplified storage of the vaccine may help in specific contexts [30]. Another focal point to reach elimination is to adapt public health strategies to local culture and customs [22] and building public confidence and demand for vaccination [38]. Awareness about the risk of rubella in pregnancy is crucial among women in childbearing age and among health care workers that must be ready to stimulate patient attention on subject. This could also help to reduce costs associated with prenatal care [14, 22, 29, 48, 71, 79]. It seems also important to establish clear serological screening guidelines including health care workers and students in training [79, 80].

Conclusions

The risk of contracting rubella in pregnancy is known, even a famous writer exploits it as a motive for a murder in her book (The Mirror Crack'd from Side to Side by Agatha Christie) [81]. However, despite the widespread awareness of its danger, there continue to be women who underestimate the risk and health care workers who do not give adequate attention to this problematic. Tools to solve this problem exist, however it is a common problem not to be able to solve it. Concrete interventions often focus on response to epidemics and are mostly short-term programs [56].

It emerges from this study that the applicable strategies are mostly known and there is an awareness of their potential functioning, however much work remains to be done to reach the goal of elimination.

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Conflict of interest statement

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Authors' contributions

EF conceived the idea of the study and supervised the working group. ET, FA, VP, LZ contributed to the literature search and the writing of the manuscript. All the

authors critically revised the manuscript and approved the final version.

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