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Descriptive Epidemiology of Rubella in Saudi Arabia: Progress Toward the 2020 Elimination Target

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An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University in partial
fulfillment of the requirements for the degree of
Master of Public Health
In Hubert Department of Global Health
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ABSTRACT

OBJECTIVE: Rubella is a mild disease with nonspecific symptoms; its significance owes to its adverse effects on pregnancy outcomes that can cause congenital rubella syndrome (CRS). Rubella is targeted for elimination in Saudi Arabia by 2020. The objective of this study is to determine the incidence and the distribution of rubella and CRS in Saudi Arabia over a 3-year period, 2013 – 2015.

METHODS: We conducted a secondary data analysis of a dataset obtained from the Expanded Program of the Immunization Department, which is housed within the Directorate of Infectious Diseases Control of the Saudi Ministry of Health.

RESULTS: From 2013 to 2015, a total of 3,193 cases of febrile rash illness were reported. Of those, there were 94 (2.9%) confirmed rubella cases. No confirmed CRS cases were reported. In 2013, the incidence rate for confirmed rubella cases was 0.22 per 100,000 population, which dropped to 0.07 in 2014 and 0.02 in 2015. The age distribution of confirmed cases was as follows: 5 (5.32%) were under 1 year, 40 (42.55%) were 1-4 years old, 19 (20.21%) were 5-19 years old, 22 (23.40%) were 20-34 years old and 8 (8.51 %) were 35-49 years old. The overall ratio of male to female was equal to one, and the majority of cases (73.40%) occurred among Saudi nationals. Approximately half of the cases (N=48) were not vaccinated, 29.79% had an unknown vaccination status (N=28), 8.51% had had their first MMR dose (N= 8), 1.06% had had two doses of the vaccine (N= 1), and 5.32% were below the vaccination age according to vaccination guidelines in Saudi Arabia (N=5). Interestingly, out of 94 cases of rubella, 15 were found to be positive for the measles immunoglobulin M (IgM) antibody.

CONCLUSION: The annual incidence of rubella in the Kingdom of Saudi Arabia in the last three years was very low (less than 1/100,000 population), and no cases of CRS have been reported since the implementation of CRS surveillance in 2013. Further studies to assess national immunization coverage and ongoing monitoring of seropositivity are necessary to evaluate progress toward rubella elimination in 2020.

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Table of Contents:

Definition of Terms

AFRO	Regional Office for Africa
CRS	Congenital Rubella Syndrome
EPI	Expanded Programme on Immunization
ELISA	Enzyme-linked Immunosorbent Assay
EMRO	Eastern Mediterranean Regional Office
IgM	Immunoglobulin M
KSA	Kingdom of Saudi Arabia
MoH	Ministry of Health
MMR	Measles, Mumps and Rubella
PCR	Polymerase Chain Reaction
RCV	Rubella Containing Vaccine
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SEAR	South East Asian region
USA	United States of America
WHO	World Health Organization

CHAPTER 1: INTRODUCTION

Overview on Rubella

Rubella is a mild acute febrile illness characterized by rash, fever and lymphadenopathy that rarely results in serious clinical manifestations (e.g. encephalitis, arthritis, and thrombocytopenia) [1]. The mild nature of the disease implies that it is often undiagnosed and under-reported [2-5]. It was first considered a public health concern in the 1940s, after the discovery of an association between rubella in early pregnancy and a set of co-occurring congenital anomalies in infants, which was subsequently named Congenital Rubella Syndrome (CRS) [3, 6]. As a result of this observation, rubella changed from being considered a mild, inconsequential disease of childhood and became a major public health concern [3]. Roughly 100,000 - 110,000 cases of CRS are estimated to occur every year, mainly in low-income countries [1, 7].

In 2012, the World Health Assembly and the Global Measles and Rubella Strategic Plan set goals for rubella and CRS elimination in at least two Word Health Organization (WHO) regions by 2015 and in at least five WHO regions by 2020 [8]. At the present time, the Americas are the only region in the world that achieved Rubella and CRS elimination.

In fact, integrating the existing, well-established elimination program of measles with the elimination program of rubella has greatly enhanced the capacity of countries to sustain the progress of rubella elimination. However, many of these countries have introduced rubella vaccine into EPI without national goals or a well-defined strategy to prevent CRS and eliminate rubella [9]. To accomplish these goals, every country should implement the WHO recommendations for strengthening their immunization services, improving surveillance, developing and maintaining outbreak preparedness, building public confidence and awareness about the demand for immunization, and conducting research to develop cost-effective action and improve vaccination and diagnostic tools [8, 10].

Today, rubella and CRS elimination—together with measles elimination—are goals throughout many countries, especially those in which the second dose of the MMR vaccine has become standard. In 2014, the WHO reported 33,068 rubella cases from 161 countries, which reflects a 95% drop from the 670,894 cases reported in 2000 from 102 countries [8].

Although much progress has occurred, rubella remains an important problem worldwide with significant public health effects. There have been several surges in rubella cases in different countries. In Japan, during the period between October 2012 and March 2014, around 15,000 cases of rubella and 43 cases of CRS were reported [11]. An outbreak of 21,283 rubella cases occurred in Poland from January to April of 2013; this was the highest number of reported cases there since 2007 [12]. In Romania, a rubella outbreak that started in September 2011 involved 1,840 probable and confirmed cases [13]. Another focal outbreak of rubella occurred in North India in April-July of 2012 and included 39 clinically suspected cases of rubella [4].

The Kingdom of Saudi Arabia (KSA) established its measles and rubella elimination program in 2008. However, case-based surveillance was established 10 years prior to that. Case-based surveillance of CRS started in 2013. The target date for Measles and Rubella Elimination is 2020 as part of the WHO-EMRO elimination plan. National disease reporting guidelines in KSA require case-based surveillance and investigation for every case of febrile rash illness. Since 2008, laboratory testing for all suspected cases of measles and rubella has been required immediately upon notification. Blood specimens and throat swabs should be collected from >80% of suspected patients with febrile rash illness. The specimens are first tested for the measles IgM antibody and, if negative, for the rubella IgM antibody by the national measles/rubella laboratory [14].

Simultaneous testing of measles and rubella was introduced in 2013, because in the 2 years before, random samples of measles-positive cases tested positive for rubella, and double infections were found in 3 samples out of the 127 tested. Shifting to simultaneous testing was also a response to the EMRO elimination target for measles and rubella. In the same year, 2013, separate investigation forms for measles and rubella were unified into one form for febrile rash illness [14].

Problem Statement

The epidemiology of rubella in KSA is not well documented, and the magnitude of reported outbreaks is probably underestimated.

The threat of rubella – and other infectious diseases for that matter – in KSA is compounded by the potential risk of widespread outbreaks during the mass gathering events of Hajj and Umrah, and by the possible importation of pathogens from neighboring countries that are experiencing unstable conditions (e.g., civil unrest), particularly Syria, Iraq, and Yemen [8]. Therefore, enhanced vigilance in surveillance is crucial.

Recently, as part of the revised plan of action for measles and rubella elimination, the KSA introduced a series of changes to strengthen its surveillance system for febrile rash illness, which is the case definition for both measles and rubella. This recent change in the rubella surveillance system requires close monitoring of rubella incidence and can be achieved by examination and exploration of the data collected by the Expanded Program of the Immunization Department.

The data obtained from the Expanded Program of the Immunization Department from 2013 to 2015 provides a unique perspective of the epidemiology of rubella in the KSA. These changes, introduced in 2013, require ongoing tracking via close monitoring of the incidence and the pattern of rubella, CRS, and dual measles and rubella infections. The only study available on rubella trends in KSA covers the period from 2009 to 2010 and identified 47 confirmed cases [2]. Since introducing the changes to the surveillance system in 2013, no study has examined rubella and CRS trends in KSA. Data from the from the MoH's EPI Department, offers a unique opportunity to assess trends in rubella and its distribution from 2013 onward. In fact, knowing the descriptive epidemiology of rubella in KSA could reflect the efficacy and progress of the immunization program implemented over 38 years ago as well as the all the elimination efforts that have been applied.

Study Purpose and Research Questions

We conducted this research to provide an update on the descriptive epidemiology of rubella in KSA We assessed rubella incidence, time trends, and distribution by person-related characteristics and geographic regions. We performed a secondary data analysis on 3,139 confirmed and suspected rubella cases reported from 2013 to 2015 to the MoH's EPI Department. Our specific research questions are:

1) What is the incidence of rubella and its time trend over a three-year period (2013 – 2015) in Saudi Arabia?
2) What is the distribution of rubella incidence by person-related characteristics and geographic regions?

Research Significance

Filling the knowledge gap in rubella incidence, trends, and distribution in KSA will offer strong support in answer to the question: does the epidemiologic profile of rubella in KSA support the possibility of rubella elimination by 2020? The study will provide insight on the efforts leading to prevention of rubella and CRS and intensify the push toward implementing policies focused on rubella elimination.

CHAPTER 2: LITERATURE REVIEW

The literature review will set the stage for the aim and the objective of the thesis. The review will first highlight the rubella and CRS background and then the epidemiological profile of both diseases. Second, it will describe the strategies for rubella prevention and its elimination program. Lastly, it will elucidate the knowledge gap concerning rubella research in the KSA and the way we must assess the epidemiological profile in the KSA.

Background on Rubella

Rubella is also known as German measles or three-day measles. This disease is often mild, with half of the people not realizing that they are sick. Transient arthralgia or arthritis are possible complications of the disease particularly among women. Other complications include thrombocytopenic purpura (occurs in approximately one in 3,000 cases) and encephalitis (occurs in approximately one in 6,000 cases) [15].

Rubella first came to the public's attention in 1881 at the International Congress of Medicine in London [3]. Before that, the disease was classified at times as measles and at others as scarlet fever. Sixty years after it first emerged at the London conference, during an epidemic of congenital cataracts in Australia, an ophthalmologist named Norman Gregg discovered an association between rubella in early pregnancy and characteristic congenital anomalies in the infants, which was subsequently named congenital rubella syndrome (CRS) [3, 6]. Cataracts, deafness, and congenital heart disease were the first recognizable signs and symptoms of CRS. In 1963, an epidemic of rubella started in Europe, spreading to the United States in 1964 and 1965 and causing severe damage in infants. Ten to twenty thousand children with congenital anomalies were accounted for as a direct result of the 1963-1964 rubella epidemic [6].

In addition to the above mentioned manifestations, CRS can result in fetal wastage, stillbirths, defects in the brain, lungs, liver, spleen, kidney, bone marrow, bones, and endocrine organs [5]. These anatomic pathologies manifest as encephalitis, mental retardation, pneumonia, hepatitis, thrombocytopenia, metaphyseal defects, diabetes mellitus, thyroiditis, patent ductus arteriosus, glaucoma, central auditory imperceptions and peripheral pulmonic stenosis. The lifelong physical and mental disability caused by CRS often requires costly institutional care and special schools. Therefore appropriate prophylaxis with a vaccine is required [1].

The other major landmark in the history of rubella was in 1962 when Weller and Neva isolated the virus from tissue culture. After this success, a rapid evolution of serologic and virology methods for studying the rubella infection took place [3]. This victory added much knowledge on the documented epidemiology and pathogenesis of rubella and permitted accurate virologic and serologic diagnosis. Many of the facts now known about rubella and CRS were identified and explained.

Rubella is transmitted through respiratory secretions and the virus is mainly present in the nasopharynx [6]. The rubella virus replicates in the throat of the person for periods of two to three weeks, known as the incubation period. The virus can be detected in blood (viremia) at high levels during the second week of infection, and this disappears upon the appearance of antibodies [6]. Sub-clinical cases account for one-third to 50% of infected individuals [6, 15]. There is a positive correlation between the presence of serum antibodies and resistance to rubella virus infection. Contracting rubella during the first trimester of pregnancy leads to an infection of the fetus through the placenta and damages 50%–90% of fetuses, with declining percentages through the second trimester. Cell death in the organs of the fetus with inhibition of cellular mitosis and vascular endothelial damage are responsible for the particular kind of damage. Babies with CRS continue to excrete the virus for months, serving as vectors of transmission of the disease to others [6].

The devastating consequences of the rubella epidemic instigated the urge to produce a vaccine. Fortunately, live, attenuated vaccines were licensed in 1969 in the United States and in 1970 in Europe [6]. The vaccines that were produced in this period had different origins, including duck embryos, dog kidneys, rabbit kidneys, and human diploid cells. But RA 27/3, the human diploid cell vaccine, was the most successful one. Over the past 30 years, the properties of the RA 27/3 vaccine have been well documented. The rubella vaccine has proven effectiveness in reducing the incidence of the disease, a single dose of the subcutaneous injection being more than 95% effective. The strain can also be given intranasal [15].

The rubella vaccine is commonly given twice in combination with the measles and mumps vaccine (MMR). After a second dose of the MMR vaccine, approximately 99% of people develop the rubella antibody and 60% have a four-fold increase in titer; still, there is no clear cut point at which vaccinated people lose protection over time or have lifelong immunity [6, 11, 15]. However, there is wide agreement that the immunity lasts for at least 20 years. Nevertheless, infections including CRS may occur in vaccinated people with low antibody titers [1].

Regarding immunity, some of the literature mentions a phenomenon called anamnestic responses that may protect the vaccinated person even if serum antibodies disappear. RA 27/3 vaccine induces IgA antibodies in the nasopharynx, which provides further protection against rubella infection [6]. The immunity of vaccinated people and the reintroduction of rubella into vaccinated populations must be further investigated [6].

About vaccine safety, seronegative adult women may develop acute transient arthralgia and arthritis after vaccination. Subclinical thrombocytopenia may also occur after vaccination. An important fact about the rubella vaccine is that the attenuated rubella virus can cross the placenta and infect the fetus, and that was lab confirmed by both cord blood antirubella IgM testing and reverse transcription polymerase chain reaction (RT-PCR) testing. However, no available data demonstrate a teratogenic risk of rubella vaccination in pregnant women [16].

In most countries, the rubella vaccine is given as MR or MMR, and the age of administration follows the schedule for measles; i.e., the first dose is usually given at 9 months or 12-15 months and a second dose at 15-18 months or 4-6 years [5].

Epidemiologic Profile of Rubella

The possible average number of transmissions from a case of rubella varies by country. In developed countries, it is between 3 and 8 cases per case. There, infections usually occur in groups of children who subsequently may infect their parents. However, the transmission of the disease among adults is also common, e.g., in military training or on cruise ships. Epidemics occur with a certain periodicity, averaging 7 years in urban areas [17].

The epidemiology of the disease differs according to the WHO region. In Europe, the number of cases reported between 2003 and 2011 decreased by 97%, from 304,390 to 9,672 case [17]. However, 2012 saw a sharp increase (about threefold) in the number of rubella cases; more than 92% of the cases occurred in Romania and Poland [12, 17, 18].

In the Americas region, the situation was ideal, as remarkable progress has been made toward the elimination of rubella and CRS. On 29, April 2015 WHO and Pan America Health

Organization (PAHO) announced that the Americas region is the first in the world to declare that its free of endemic transmission of rubella [19]

In the Africa region (AFRO), an estimated 22,000 children were born with CRS in 1996, and about 46,000 in the South East Asia region (SEAR) [17]. By 2012, few countries in AFRO and SEAR had introduced RCV in their national immunization policies; therefore, the current status in those two regions is thought not to have changed in comparison to 1996 [17]. In another study, the incidence in both regions registered a 20-fold and 14-fold increases in rubella cases between 2000 and 2009 [20]

In the Western Pacific region, the estimated number of cases in 1996 was close to 13,000 [21], and the region set the goal to reduce the prevalence of rubella and CRS to < 1 case per 100,000 by 2015 [22, 23].

Finally, in the Eastern Mediterranean region (EMRO), 16 of 22 countries have introduced the rubella vaccine into their vaccination schedules and 13 have implemented a national target for rubella and CRS elimination [17]. However, the EMR registered a 35% reduction in rubella cases between 2000 and 2009 [20].

Strategies for Rubella Prevention and Elimination

The most important means of rubella prevention and elimination are maintaining a high population immunity with excellent vaccination coverage and a high-quality, sensitive surveillance system [8].

Regarding vaccination, approaches vary between countries, depending on the epidemiological profile and other economic issues. For every approach, there are challenges and limitations. For example, including RCV in routine childhood vaccination schedules alone is a beneficial and cost-effective approach to eliminating rubella and CRS [24]. However, there is a significant strategic issue that could occur called the “paradoxical effect,” when countries aim to vaccinate only infants and fail to maintain the level of vaccination coverage at over 80% [20], thereby increasing the susceptibility of pregnant women to residual exposures during later pregnancy [6]. This fact creates a unique policy problem in low and middle-income countries because the rubella immunization programs need to achieve herd immunity and coverage rates above 80%, and the majority of these countries are unable to sustain this coverage standard [20]. Even though the paradoxical effect is temporary and with time the infants become immunized adults, it is better to deal with this temporary effect by implementing a mass vaccination campaign targeting women (or both sexes) up to 39 years of age [6, 25]. A catch-up campaign of children also effectively reduces the risk of a paradoxical effect [6].

Others types of vaccination program strategies, include the vaccination of specific high-risk groups such as health workers, children, and females in childbearing age [26, 27].

In general, rubella vaccination strategies are more cost-effective and have a higher cost benefit ratio in high- and middle-income countries in comparison to CRS’s economic cost [24, 28].

A historical review of rubella vaccination strategies implemented in the United States and the United Kingdom can give us clues about the best strategies that should be implemented to eliminate rubella [6]. Initially, there were different approaches for the vaccination program in these countries. In the United States, the vaccination program focused on infants mainly, while in the United Kingdom, it was primarily concerned with adolescent girls. Both strategies were partial successes. In the United States, pregnant women were still at risk, and in the United Kingdom, girls who refused vaccination were at risk of contracting rubella from men and other children [6].

As a result of these gaps in both programs, each country changed its strategy to a more comprehensive one, focusing on interrupting rubella virus transmission and eliminating rubella and CRS by including both universal immunization of infants and targeted vaccination of adolescent girls and adult women.

In accordance with this history, the gold standard strategy for the elimination of rubella and the prevention of CRS is the combination of routine childhood vaccinations and the mass vaccination of all males and females up to 39 years of age [6].

There is widespread agreement that these approaches are better than routine childhood vaccination alone or in combination with immunization of just selective categories of the adult population (such as postpartum vaccination for women who test negative for rubella in antenatal screening [29], high risk groups such as military recruits, and health care workers) [6]. However, there is evidence that postpartum vaccination can significantly reduce the number of women susceptible to rubella infection [30, 31].

The main factor supporting the rubella elimination effort is the presence of a strong commitment toward the worldwide measles elimination program. Many of the key components of the measles elimination program are critical factors in rubella and CRS elimination: high routine immunization coverage with two doses of MMR vaccine, nationwide vaccination campaigns, and high epidemiologic surveillance for febrile rash illness. In addition, the clinical symptoms of rubella and measles are similar and both affect the same age groups [17]. In fact, the importance of rubella elimination became evident when laboratory studies of the rash related to the measles elimination campaigns revealed a high prevalence of rubella virus infections. This encouraged countries in the Western Hemisphere to adopt rubella and CRS elimination, which was supported by the Pan American Health Organization [6].

Elimination of rubella and CRS is now a goal throughout many countries, together with measles elimination [6]. Although the WHO has set a goal of rubella eradication by 2020, not all countries have included the rubella vaccine in their national immunization programs. In 2011, 130 countries did so [32].

In terms of the goal of eliminating rubella, it critical that all countries implement case-based surveillance to detect, investigate, and confirm every suspected measles and rubella case in the community, in addition to having a good vaccination program [6]. A great example of the rubella elimination is Finland, which has been a leader in this respect. Finland's successes depend mainly on the maintenance of high coverage and monitoring by serologic testing [6]. Furthermore, the United States experience of elimination of rubella and CRS can be a good lesson for application in other developing countries like the KSA.

The United States increased MMR vaccination coverage in the early 1990s by adding a universal second dose. In addition, the efforts of Mexico and other Latin American countries to vaccinate against rubella have reduced the introduction of rubella virus across the border into the United States. As a result of good vaccination coverage and a sensitive surveillance system, in 2004, a committee of experts from the Centers for Disease Control and Prevention decided on the basis of clinical, laboratory, and epidemiological evidence that rubella was no longer endemic in the United States. Each year from 2005 to 2011, a median of 11 rubella cases was reported in the United States, with a total of 67 rubella cases. Over the same period, two rubella outbreaks involving three cases and four total CRS cases were documented [15]. Of these, 28 (42%) were known importations [15].

The European Region of the WHO (EURO) has also started on the elimination of rubella. While northern Europe attempted the job, southern and Eastern Europe still suffer from low vaccination rates, which results in persistence of the disease [6].

Behind the optimistic vision of rubella elimination around the world is the example of several countries where it has been accomplished, such as the United States and other developed countries. There is hope that one day this threat to healthy infants will be completely eradicated.

The Status of Rubella in KSA

In KSA, rubella outbreaks are not documented and the incidence of CRS is not well known. However, the KSA has joined in the worldwide commitment to rubella control, elimination, and eventual eradication effort announced by WHO.

In the KSA, the rubella vaccine was first introduced in 1978. The initial rubella vaccination policy targeted schoolgirls (11–14 years) to protect their future pregnancies [2]. In 1982, the MMR vaccine was licensed and offered to all children of both sexes at 12 months of age, as well as to prepubescent girls [2]. In 1991, KSA implemented the expanded program on immunization (EPI) [2]. Since then, the rubella vaccine has been given as part of the MMR vaccination national immunization program. The EPI schedule has been changed several times with the aim of ensuring high immunity and coverage. Recently the MMR vaccine has been given to all children at 12 ,18 months of age, and while at school [2]. The goal of a childhood rubella vaccination program is mainly the prevention of intrauterine rubella infections by eliminating the circulation of the rubella virus in the community, protecting pregnant women. To accomplish this goal, childhood vaccination programs should achieve vaccination coverage of 80% and above [33]. A mumps-measles–rubella vaccination campaign targeted both gender aged between 6 months and 18 years was conducted in 2011 to interrupt measles and rubella transmission in KSA.

In response to WHO recommendations, the surveillance system in KSA adopted the immediate notification of any case of febrile rash illnesses. Any suspected case requires obligatory immediate notification (within 24 hrs.) from health centers, clinics, and hospitals to the Regional Directorate of Health Affairs and then to the MoH. In addition, active surveillance conducted at regional levels is carried out to intensify the surveillance system. National health authorities in KSA have recommended case-based surveillance and epidemiological investigation of every suspected case within 48 hours.

Furthermore, in order to accelerate measles and rubella elimination and improve CRS prevention, since 2013 the Saudi national laboratory has adopted laboratory testing for all suspected cases of measles and rubella (febrile rash illness), which are required immediately upon notification. The laboratory test is done simultaneously for both rubella and measles. Following WHO guidelines, both serum sample and throat swab are collected from each suspected case at first contact with a health facility and sent to the national laboratory in Riyadh to detect rubella-measles IgM antibodies using standardized, validated, and rapid Enzyme-linked Immunosorbent Assay (ELISA) IgM assays. The suspected cases are confirmed in the national laboratory by a positive serological test for rubella-specific IgM antibodies or positive polymerase chain reaction (PCR). Furthermore, in 2013 the case based surveillance of CRS were established.

High-quality rubella and CRS surveillance are necessary to assess the role of rubella vaccination programs and verify the achievement of rubella and CRS elimination goals. Regular monitoring of measles and rubella rates via surveillance data is also important to identify geographic areas and populations with low immunity and are at greater risk of developing rubella so that prevention, control, and elimination efforts can be directed toward them.

CHAPTER 3: MANUSCRIPT

Descriptive Epidemiology of Rubella in Saudi Arabia: Progress Toward the 2020 Elimination Target.

Abstract

OBJECTIVE: Rubella is a mild disease with nonspecific symptoms; its significance owes to its adverse effects on pregnancy outcomes that can cause congenital rubella syndrome (CRS). Rubella is targeted for elimination in Saudi Arabia by 2020. The objective of this study is to determine the incidence and the distribution of rubella and CRS in Saudi Arabia over a 3-year period, 2013 – 2015.

METHODS: We conducted a secondary data analysis of a dataset obtained from the Expanded Program of the Immunization Department, which is housed within the Directorate of Infectious Diseases Control of the Saudi Ministry of Health.

RESULTS: From 2013 to 2015, a total of 3,193 cases of febrile rash illness were reported. Of those, there were 94 (2.9%) confirmed rubella cases. No confirmed CRS cases were reported. In 2013, the incidence rate for confirmed rubella cases was 0.22 per 100,000 population, which dropped to 0.07 in 2014 and 0.02 in 2015. The age distribution of confirmed cases was as follows: 5 (5.32%) were under 1 year, 40 (42.55%) were 1-4 years old, 19 (20.21%) were 5-19 years old, 22 (23.40%) were 20-34 years old and 8 (8.51 %) were 35-49 years old. The overall ratio of male to female was equal to one, and the majority of cases (73.40%) occurred among Saudi nationals. Approximately half of the cases (N=48) were not vaccinated, 29.79% had an unknown vaccination status (N=28), 8.51% had had their first MMR dose (N= 8), 1.06% had had two doses of the vaccine (N= 1), and 5.32% were below the vaccination age according to vaccination guidelines in Saudi Arabia (N=5). Interestingly, out of 94 cases of rubella, 15 were found to be positive for the measles immunoglobulin M (IgM) antibody.

CONCLUSION: The annual incidence of rubella in the KSA in the last three years was very low (less than 1/100,000 population), and no cases of CRS have been reported since the implementation of CRS surveillance in 2013. Further studies to assess national immunization coverage and ongoing monitoring of seropositivity are necessary to evaluate progress toward rubella elimination in 2020.

Introduction

Rubella, or German measles, is a viral infection that presents as a mild febrile rash illness in adults and children with about 20%-50% of infected persons being asymptomatic[34]. However, rubella can have severe adverse effects on the fetuses of pregnant women who contract the disease, especially during the first trimester of pregnancy, causing a broad range of congenital defects known as Congenital Rubella Syndrome (CRS) [5, 7, 17, 34, 35]. Besides the devastated outcome of CRS, the estimated lifetime cost of treating one child with CRS in high-income countries is over $140,000 [28].

Fortunately, rubella is a vaccine-preventable disease, and the rubella vaccine has proven highly effective; a single dose of the vaccine is more than 95% effective [29, 34].

In 2012, the World Health Assembly and the Global Measles and Rubella Strategic Plan set goals for rubella and CRS elimination in at least two Word Health Organization (WHO) regions by 2015 and in at least five WHO regions by 2020 [8]. In 2015, the Americas region was the first in the world to eliminate rubella and CRS. Today, rubella and CRS elimination—together with measles elimination—are goals throughout many countries, especially those in which the second dose of MMR vaccine has become standard [36].

Although much progress in the field of control and elimination of rubella has occurred, rubella remains an important pathogen worldwide with harmful effects: roughly 100,000 to 110,000 cases of CRS are estimated to occur every year, mainly in low-income countries [1, 7]. In addition, there have been several surges in rubella cases in different developed and developing countries such as Japan, Romania, and India [11, 13, 37]

The KSA established its measles and rubella elimination program in 2008. The elimination target date is 2020 as part of the EMRO elimination plan. The MoH's Expanded Program on

Immunization (EPI) Department requires case-based surveillance, case investigation, and laboratory confirmation for every case of febrile illness with rash [14].

Close monitoring of the incidence and pattern of rubella and CRS are required in KSA. There have been no recent studies on the epidemiology of rubella and CRS; the most recent covers the period of 2009 to 2010, before changes to strengthen the rubella surveillance system were implemented in 2013.

To offset this gap, we conducted a secondary data analysis using data from the MoH's EPI Department to assess the descriptive epidemiology of rubella and answer these specific research questions: What is the incidence of rubella in KSA and its time trend over a three-year period, 2013 –2015? What is the distribution of rubella incidence by person-related characteristics and geographic regions?

Answering this research question will provide a strong background for answering the question: does the epidemiologic profile of rubella in KSA support the possibility of rubella elimination by 2020? This study will provide insight into the efforts leading to prevention of rubella and CRS and intensify the push toward implementing policies focused on rubella elimination.

Methods

Study Setting

Measles, Rubella and CRS Elimination Program in KSA

KSA launched its EPI in 1991 year; through efforts of the program, the national vaccine coverage rate is now at more than 90% for the majority of vaccine-preventable diseases. For example, the overall vaccination coverage of MMR in 2014 was 97%[38].

In 2008, under the regulation of the EPI program, KSA introduced its plan to eliminate measles, rubella and CRS by 2015. The plan's target date was revised to 2020. Since then, several initiatives have been launched to accomplish this goal, including ensuring high population immunity, strengthening the surveillance system, improving case management, and limiting transmission. To ensure high population immunity, KSA has improved coverage with two doses of MMR and reached 95% of the population or more in all regions.

To strengthen the surveillance system, both active and passive surveillance have been applied. To improve case management, a minimum of 80% of all reported suspected measles cases should be adequately investigated within 48 hours of notification. In addition, specimens adequate for detecting acute measles or rubella infection should be collected from at least 80% of suspected measles and rubella cases and tested in a proficient laboratory.

To limit transmission, public health awareness campaigns have been implemented and contacts vaccinated when needed.

Data Source

The dataset for this study was obtained from the MoH's EPI Department, housed within the Directorate of Infectious Diseases Control. The EPI Department runs the measles, rubella, and congenital rubella elimination program. The dataset contains individual-level epidemiologic and laboratory information on all cases of febrile rash illness (i.e. Suspected rubella cases), reported from 2013 to 2015. The source of the information for the dataset was the notification reports completed for each identified case, collected at the regional level, and submitted through the MoH's EPI Department.

At the level of the MoH, data was entered in such a way that each record represents a case with its clinical, laboratory, and epidemiologic data.

The dataset included 3,193 cases of febrile rash illness that met the case definition used for the measles and rubella elimination program.

To calculate incidence rates, we obtained population data to use as the denominator from two sources: 1) the Saudi Central Department of Statistics (CDS), which draws statistical information from the census, field surveys, and statistical studies, and 2) the MoH statistical book, which provides population data stratified by region.

Case Definition

Rubella Case Definition

A case of rubella or measles is defined by the Measles and Rubella Elimination Program as any person with fever and rash or one in whom the healthcare worker suspects measles or rubella. Using this case definition ensures standardized reporting of cases across health facilities all over KSA, and avoids missing cases of rubella due to its high sensitivity. This helps accelerate the elimination of rubella as well as maintain a rubella incidence of zero cases per year, after excluding cases confirmed as imported.

An imported rubella case is defined as a case exposed outside of the country or region from 12 – 23 days before rash onset, as supported by epidemiological or virological evidence or both. A confirmed case is any case with positive anti-rubella antibodies (IgM), as assayed by enzyme-linked immunosorbent assay (ELISA).

Congenital Rubella Syndrome Case Definition

Clinical case: An infant with no other defined etiological explanation in whom a physician detects at least two of the clinical features in group A or one from group A and one from group B. Group A signs and symptoms include: Cataract(s), congenital glaucoma, congenital heart disease, hearing impairment and pigmentary retinopathy. Those for Group B include: Purpura, splenomegaly, microcephaly, mental retardation, meningoencephalitis, radiolucent bone disease, jaundice

Laboratory-confirmed case: An infant having at least one clinical feature listed in group A and meeting the laboratory criteria for congenital rubella infection.

Epidemiologically linked case: An infant with at least one clinical feature from group A and whose mother had confirmed rubella during pregnancy.

Study Variables

The variables in the dataset included demographic characteristics (age, gender, nationality, and region), month of reporting, clinical date (signs, symptoms and complication), vaccination status and travel history (12-23 days before rash onset).

Data Management

We received the initial dataset as two separate Excel files, one for the line list of suspected and confirmed febrile rash illness cases for 2013, and the other for the 2014 – 2015 line list. The analysis focused on the years 2013 to 2015 for two reasons: 1) the change in case definition resulted by the introduction of simultaneous testing for measles and rubella in 2013, and 2) inconsistencies in the format and structure of the data collected before and after 2013.

Prior to analysis, the datasets were thoroughly examined for inconsistencies, inaccuracies, and invalid entries. During this examination and subsequent data cleaning process, several variables were reclassified or recoded for inaccuracies. First, some of the data were in Arabic (e.g., month, clinical profile, complications) and required translation to English. A bilingual ESL instructor at Emory University validated the Arabic to English translation. We also reoriented the dataset sheets to be read from right to left. Second, the age variable was recoded into six age groups (less than 1 year old, 1-4, 5-19, 20-34, 35-49 and 50 or older). Third, the region was changed from the 20 health regions of KSA into the 13 administrative regions, for consistency with the available population data. Some of the variables (signs and symptoms, complications, travel history, and disease outcome) were only available for 2014 and 2015.

Despite the fact that people's vaccination status was routinely determined from the PHC registry, vaccination card, and/or the parent, we found inaccuracies regarding vaccination status, e.g., suspected cases over the age of 1 year old being classified as "not reaching the recommended age for vaccination" despite their age eligibility (N=20). In response to this issue, we censored these variables from the corresponding analysis. In addition, two-dose MMR vaccination status for the year 2013 was not included in that dataset. Data cleaning and translation was conducted in Microsoft Excel 2010 (Microsoft, Seattle, WA).

Statistical Analysis

Incidence rates (IR) for rubella per 100,000 population were calculated over a 3-year period (2013 – 2015), and region-, gender- and nationality-specific rates were estimated. Rates were compared using 95% confidence intervals. We calculated the proportion of confirmed cases of rubella and used the febrile rash illness cases as the denominator, distributed by the same variables mentioned above. Further exploratory analyses of the data were done to produce summary statistics for independent variables such as the demographic (gender, age, nationality) and clinical (complication and vaccination status) variables. Frequency counts and percentage of subjects within each category were summarized for categorical data.

Ethical Considerations

This study was determined by the Institutional Review Board of Emory University to be exempt from review because it is an analysis of secondary data and all data were de-identified prior to use by the researcher.

Results

Incidence Rates and the Proportion of Confirmed Rubella Cases

From 2013 to 2015, a total of 3,193 cases of febrile rash illnesses were reported, of which a total of 94 rubella cases were confirmed (2.9%); there were no reported confirmed cases of CRS.

The IR for confirmed rubella in 2013 was 0.22 per 100,000, which dropped to 0.07 per 100,000 in 2014 and 0.02 per 100,000 in 2015 (Table 1).

An assessment of the proportion of confirmed rubella among the cases of febrile rash illness over time shows a constant reduction: in 2013, the proportion of confirmed cases was 5.33%, dropping to 2.76% in 2014, and to 0.45% in 2015 (Table 2).

Stratified by gender, no statistically significant differences in the IR of confirmed rubella cases among the population were observed. In 2013, the IR (per 100,000) was 0.20 among males and 0.25 among females (p-value=0.40); in 2014, the IR was 0.05 among males and 0.11 among females (p-value=0.10); and in 2015, the IR was 0.02 among males and 0.01 among females (p-value=0.34) (Table 3).

In addition, there was no statistically significant difference in the proportion of confirmed rubella cases among febrile rash illness by gender; in 2013, the proportion of rubella cases was

5.46% for males and 5.48% for females (p-value=0.99); in 2014, it was 1.92% for males and 3.90% for females (p-value=0.089); and in 2015, the proportion was 0.67% for males and 0.19% for females (p-value=0.27) (Table 4).

Stratified by nationality, no statistically significant differences were observed in the IRs of confirmed rubella cases between Saudis and non-Saudis; in 2013, the IRs (per 100,000) were 0.24

for Saudis and 0.17 for non-Saudis (p-value=0.25); in 2014, they were 0.07 for Saudis and 0.08 for non-Saudis (p-value=0.82); and in 2015, they were 0.02 for Saudis and 0.00 for non-Saudis (p-value=0.28) (Table 5).

Neither did we find any statistically significant differences by nationality in the proportion of confirmed rubella cases among febrile rash illness; in 2013, the proportion of rubella cases was 5.02% for Saudis and 6.67% for non-Saudis (p-value = 0.32); in 2014, it was 2.36% for Saudis and 4.15% for non-Saudis (p-value=0.21); and in 2015, it was 0.55% for Saudis and 0.00 for Non-Saudis (p-value=0.03) (Table 6).

Descriptive Epidemiology for Confirmed Rubella Cases

Age Distribution

A total of 94 cases were confirmed during the period from 2013 – 2015. The age distribution of confirmed cases was as follows: 5 (5.32%) were under 1 year of age, 40 (42.55%) were 1-4 years old, 19 (20.21%) were 5-19 years, 22 (23.40%) were 20-34 years and 8 (8.51%) were 35-49 years (Table 7).

Gender Distribution

The overall ratio of male to female was equal to one; however, variations in the gender composition of cases were seen over the years (Table 7). The percentage of males was higher (51.52%), while in 2014, females constituted the largest proportion (60.87%). In 2015, four cases out of five (80%) were male (Table 7).

Nationality Distribution

In general, the majority of cases occurred among Saudi nationals (69, 73.40%) and the rest among non-Saudis (25, 26.60%). In 2013, Saudis cases numbered 49 (74%) out of 66. In 2014, they numbered 15 (65.22%) out of 23, and in 2015, all five cases were Saudi (100%) (Table 7).

Geographical Distribution

Makkah region reported the highest number of rubella cases (32, 34.04%), followed by Riyadh (24, 25.53%), then Eastern region (14, 14.89%), Al-Medinah (7, 7.45%), Najran (7, 7.45%), Al-Qasim (5, 5.32%), Hail (2, 2.1%), Northern Borders (2, 2.13%), Al-Baha (1, 1.06%). (Table 8). Four regions, Al-jouf, Assir, Jazan and Tabuk, did not report any confirmed cases of rubella.

Travel history to indicate which cases were imported was only included in 2014 and 2015. Four (14.3%) out of 28 rubella cases had travelled during the 12-23 days before the rash's onset while the rest (85.7%) were local residents who contracted the infection within the country

Seasonal Distribution

Although rubella cases occurred throughout each year, their distribution was characterized by peaks in the late winter and early spring. The disease frequency peaked in April (24.47%), followed by May (15.96%) and then March (12.77%) (Figure 1).

Vaccination Status Distribution

The vaccination status was available for 90 out of 94 cases. More than half of the cases 48 (51.06%) were not vaccinated, while 28 (29.79%) cases were unknown, 8 (8.51%) had had the first MMR dose, 1 (1.06%) case was vaccinated with two doses, and 5 (5.32%) were below the vaccination age according to the KSA vaccination status (Table 9).

Clinical Characteristics of Confirmed Rubella Cases

Clinical manifestation and travel history were new variables added to the surveillance system in 2014 and 2015 and were not available before. Besides the febrile rash illness that is a common manifestation of all confirmed cases, there were several other clinical manifestations. Among the 28 confirmed in 2014 and 2015, half of the cases 14 (50.0%) reported sore throat, 10

(35.7%) reported cough, 8 (28.6%) Coryza, 5 (17.9%) conjunctivitis, and 4 (14.3%) koplike spots (Table 10). There were no reported complications among the cases, nor any reported deaths.

Interestingly, among all 94 cases of rubella, 15 cases were also found to be positive for measles IgM antibody. Among those, six cases (40%) were 1-4 years old, 10 (66.67%) were Saudi, 9 (60%) were female, majority (46.67%) were from Makkah region, and above half of them (53.33%) unvaccinated (Table 11).

Descriptive Epidemiology for Febrile Rash Illness Cases

Age Distribution

There were a total of 3,139 cases of febrile rash illness during the period from 2013 – 2015. The age distribution of confirmed cases was as follows: 369 (11.56%) were under 1 year of age, 936 (29.3%) were 1-4 years old, 778 (24.37%) were 5-19 years, 741 (23.2%) were 20-34 years, 220 (6.89%) were 35-49 years, 38 (1.2%) were over 50 years old, and for 111 (3.48%), no age data was available (Table 12).

Gender Distribution

In general, the overall ratio of males to females with the illness was 1:2. In 2013, 47.38% of those with febrile rash illness were women and 50.77% were men; in 2014, 43.15% were women and 56.37% were men; and in 2015, 46.35% were women and 53.57% were men (Table 12).

Nationality Distribution

Of febrile illness cases, 660 (20.67%) were non- Saudi and 2,528 (79.17%) were Saudi. One person (0.03%) did not specify a nationality and 4 (0.13%) had no available information for them (Table 12).

Geographical Distribution

The geographical distribution of cases across the 13 administrative regions shows that the majority were reported from Makkah region (881, 27.6%) followed by Riyadh (872, 27.3%), Eastern region (423, 13.2%), Al Madinah (5.8%), and Najran (5.4%) (Table 8).

Seasonal Distribution

Although febrile rash illness cases occurred throughout each year, they were characterized by peaks in the late winter and early spring. The peak frequency of the disease occurred in May (12.65%), followed by April (11.93%), then June (10.55%) (Figure 2).

Vaccination Status Distribution

Vaccination status was available for 2,242 cases. Out of these, 685 (30.6%) were not vaccinated, 572 (25.5%) were vaccinated with the first MMR dose, and 359 (16.0%) cases were vaccinated with two doses. There were 325 (14.5%) cases who were below the vaccination age, and 301 (13.4%) had unknown vaccination status. Examining vaccination status by year reveals a steady increase in the proportion of cases vaccinated by one dose or more, and a steady decrease in the unvaccinated proportion (Figure 3).

Discussion

The annual incidence of rubella in KSA from 2013 to 2015 was very low (less than 1/100,000 population), and no cases of CRS were reported since the implementation of CRS surveillance in 2013.

In 2013, the incidence rate for confirmed rubella was 0.22 per 100,000 population, which dropped to 0.07 per 100,000 in 2014 and 0.02 per 100,000 in 2015. However, the burden of rubella in KSA before this period was not well known, which made following the trend of the disease in the previous years difficult.

In 2008, KSA established a goal for the elimination of measles and rubella by 2015 as a part of the WHO EMRO elimination plan [39]. A new target for elimination has been set for 2020. Despite missing the 2015 goal, our results provide encouraging evidence that elimination is attainable by, if not before, the 2020 target.

The low incidence of rubella in KSA over the period of 2013 to 2015 reflects the progress made by the immunization program and elimination efforts over time, and also their remaining challenges.

KSA has succeeded in maintaining the rubella IR at <1 case per 100,000 in the last few years. In 2012, the IR reported in the national health statistics report was 0.06 per 100,000. In 2013, we observed a slight increase in IR to 0.22 per 100,000, a likely artifactual increase owing to the introduction of simultaneous measles-rubella testing and the corresponding change in the case definition of confirmed rubella. Our study confirmed that the trend in rubella incidence continued to decrease in 2014 (0.07 per 100,000) and 2015 (0.02 per 100,000). In fact, the 2015 rate constitutes the lowest reported over the last 4 years. This is a clear demonstration of the success of national efforts invested in strengthening the surveillance system and ensuring a high vaccine coverage rate for MMR.

In conjunction with the decreasing rates of rubella, our study observed a concomitant decrease in the proportion of confirmed rubella among febrile rash illnesses. In 2013, the percentage of confirmed cases was 5.33%, which dropped to 2.76 % 2014, and to 0.45% in 2015. When the prevalence of rubella is low, the proportion of true rubella among suspected cases meeting the case definition is low; this demonstrates that besides making good progress towards elimination, that the sensitivity of the rubella surveillance system is also high.

When we compared our results with those of the study that covered the period from 2009–2010, we noticed that the epidemiological characteristics of rubella from 2013–2015 were not substantially different except for the geographical distribution and vaccination status.

During the period from 2013–2015, the annual number of case ranged from 5 to 66 cases, with a total number of 94 cases. That was similar to the rubella data that were available from the 2009 – 2010 study, with a total of 47 laboratory confirmed cases reported [40]. Also, the 2012 statistic showed 18 cases, which falls within the same range [38].

In both the previous study covering the period 2009- 2010 and the present analysis, the ratio of males to females was equal to one, which is somewhat different than the recent rubella outbreaks that show a slightly to moderately higher male ratio [11, 12]. This may be explained by the fact that the immunization program targets all children equally, and no current specific programs target women of childbearing age similar to other countries.

In the current analysis, 42.55% of cases were children 1-4 years of age, and that was similar to the period 2009-2010, during which children 1-4 years constituted a larger proportion of the cases 54% [40].

In fact, since 2013, the cohort of children aged 1-4 years have been receiving two doses of MMR according to the vaccination policy in KSA, and that may be one of the reasons for the overall reduction in rubella cases [14].

There were no documented percentages for the other age groups in the 2009 – 2010 study, but the current analysis showed that cases aged 20 years and above constituted about one-third of the cases (31.9%). This finding is significant because it pinpoints the susceptibility of this age group for rubella and is worthy of ongoing monitoring, especially since several countries have started to report a shift in rubella occurrence to the older age groups [37]. The shifting in incidence to an older age group reflects susceptibility due to lack of exposure to the virus in childhood or lack of vaccination due to changes in the vaccination schedule.

Another interesting finding is that 5.32% of the cases were under one year of age and therefore not due for vaccination according to KSA’s national vaccination program [14]. Further investigation of this finding is required to see if it is reflective of a weaning passive immunity from the mother or a lack of immunity in the mother.

This study also demonstrates regional differences in the distribution of rubella cases in comparison to the distribution of cases from 2009-2010. In this study, the highest proportion of the cases was from Makkah region (34.0%), followed by Riyadh region (25.5%), and Eastern province (14.9%) In 2009-2010, Riyadh region constituted the largest proportion of cases (29%), followed by Eastern province (12.7%) [40].

The change in geographic distribution could be attributable to the optimization of the surveillance system in the Makkah region to meet the unique requirements of Hajj and Umrah and lower the risk of infectious disease introduction. Hajj usually attracts 2-5 million Muslims for pilgrimage from numerous countries. For this, KSA invests in ensuring a good surveillance system to contain infectious diseases and maintain the wellbeing of pilgrims [41].

There were four regions in KSA that registered no rubella cases over the last three years, which requires further verification of the absence of the disease in this region. Maybe these regions experience reporting challenges such as lower levels of health worker awareness and different health-seeking behavior of the population. Results can be verified by reviewing the regional surveillance indicator for each region and the vaccination coverage rate of the MMR vaccine.

The data in the present study demonstrated a similar seasonality pattern to 2009-2010: although rubella infections occurred throughout each year, they were characterized by peaks in the late winter and early spring. The peak of the disease was in April in both the present (12.7%) and previous analysis (26.67%).

Our findings highlight the important role of vaccination status in preventing the infection; about 9.57% of cases were previously vaccinated, while approximately half of the confirmed rubella cases occurred among unvaccinated people, a finding that is expected and confirmed by other studies [11-13]. On the other hand, in the 2009-2010 study we observed that 32% of the cases occurred among the vaccinated population, compared to 28% among unvaccinated population; that difference between the current and previous analysis may be due to the improvement in documentation of the vaccination status over the last years, which was expressed by the low percentage of unknown vaccination status (13.4%) in the present study compared to 40.4% in the 2009-2010 study [40]. The low percentage of cases among the vaccinated population in the present analysis demonstrates the efficacy of the rubella vaccine besides proper vaccine handling and storage. In addition, the absence of reported outbreaks or epidemic transmission is further evidence of the activity of a vaccine that just requires a 83–85% herd immunity threshold to interrupt rubella transmission (compared with 92–94% for measles) [42].

The results of this study show that the proportion of unvaccinated people has decreased, but the fact that 28.1% of the unvaccinated were women of reproductive age (20-49 years) could be a huge risk for the development of CRS in the future. Although children aged 1-4 years old were the main group infected by the rubella virus, they probably had come into contact with a susceptible pregnant woman and exposed her to the virus. A possible intervention to reduce the number of susceptible subjects and the continuing circulation of the virus would be the vaccination of women of childbearing age who had not been vaccinated before or showed no immunity in the rubella anti-natal screening test [2]. These women can be reached when they have any contact with the health system.

Another important finding was obtained from travel histories over the last two years (2014-2015): the majority of cases do not have travel histories, which indicates the existence of transmission of indigenous and imported rubella virus in the community.

Interestingly, the simultaneous testing of the serum samples for rubella and measles revealed the presence of cases of dual infection. In 2013 six cases were reported as dual infection of measles and rubella, in 2014 there were eight reported cases and one case was in 2015. The dual infection phenomena has not been well described in the literature or in KSA [40] , however, mixed measles and rubella outbreaks are a common phenomenon reported in different countries [43, 44].

A limitation in our study is data completeness and quality. The database available at the level of MOH is rich and has valuable information but, unfortunately, they were the issues of missing and incomplete data. However, the availability of monthly data, in addition to annual occurrence, and the fact that data covered all the KSA are strengths of this study.

Further improvement in the data documentation and management are recommended to ensure more comprehensive data collection in surveillance system. Laboratory confirmation is a critical component of any elimination program. However, efforts are needed to improve diagnostic procedures. Isolation of the virus and further sequencing of nucleic acid might provide further sensitivity for the surveillance system as well as useful information on the origin of the circulating virus and confirm the imported cases.

Overall, our study observed a low incidence of rubella in KSA, indicating that progress toward the 2020 elimination target is underway. Our study provided a background for further research and has implications on strengthening the rubella elimination program and surveillance efforts.

CHAPTER 4 – CONCLUSION AND RECOMMENDATIONS

The annual incidence of rubella in the KSA in the last three years has been reduced to less than one per 100,000 population. As well, no cases of CRS have been reported in KSA since the implementation of the program in 2013 [14]. However, the epidemiological profile of the disease indicates the persistence of endemicity in KSA, and that there is a slight shift of cases towards the adult population.

In addition, despite the steady improvement in vaccination status, a substantial proportion of the febrile rash illness cases were not vaccinated or their vaccination status was poorly documented.

The study also demonstrated variations in geographical distribution, which requires different strategies for each region. Regions that did not register any cases over the last three years require further investigation to verify the zero reports and determine whether they require additional strengthening of their surveillance program. The regions that showed higher incidence rates should assess their vaccination coverage and identify susceptible populations as soon as possible.

This study shed light on the presence of women of childbearing age who had not been vaccinated. To remedy this gap, women in this category should be targeted for vaccination services when they visit health providers for any reason in primary health care centers or private hospitals. Antenatal programs would be especially effective at targeting this group.

Based on our findings and those of other studies, KSA has made good progress towards the elimination of rubella and CRS. The accelerated rubella elimination is feasible within the framework of integrated measles–rubella and CRS elimination strategies. To reach the target date set by KSA to eliminate rubella in 2020, an enhanced surveillance system should be implemented to ensure that all reported cases are laboratory confirmed, that rubella virus strains are isolated and genotyping is carried out to provide evidence for the interruption of endemic transmission through the detection of all imported and import-related cases, and to verify the absence of endemic measles–rubella strains. In addition, CRS surveillance should be evaluated and strengthened.

Further studies assessing the national immunization coverage and the periodic monitoring of seropositivity should be carried out as a means of detecting whether vaccine-induced immunity in highly vaccinated cohorts is waning and identifying the current gaps and further steps to be taken to achieve the targets. The high immunization coverage (95%) incorporating two doses of MMR vaccine should be maintained, and periodic follow-up immunization campaigns may be also needed.

In summary, to achieve the 2020 elimination target, we recommend the following:

1. Maintain high population immunity with excellent immunization coverage by ensuring high vaccine coverage in children to minimize rubella virus circulation in the younger age groups.
2. Develop a mass vaccination campaign to be implemented throughout the country, using measles–rubella-containing vaccines and targeting both women and men age <40 years
3. Rigorously analyze the surveillance and vaccination coverage data to determine the effectiveness of the campaign.

4. Focus on obtaining accurate molecular epidemiology data from confirmed cases to assist in determining which isolates are endemic and which are imported.
5. Target the most vulnerable populations (females of childbearing age) using the data from the national surveillance system and antenatal screening program.
6. Conduct further studies to characterize the rubella genotypes, vaccine coverage rate, and surveillance quality.

Tables and Figures

Table 1. Incidence of Confirmed Rubella by Year, Kingdom Of Saudi Arabia, 2013 – 2015

Year	Rubella	Total population	IR°	95% CI*	
				Lower	Upper
2013	66	29994272	0.22	0.17	0.28
2014	23	30770375	0.07	0.05	0.11
2015	5	31521418	0.02	0.01	0.03
Total	94				

°IR = incidence rate per 100,000 population

*CI = confidence interval

Table 2. Percentage of Confirmed Rubella among Cases of Febrile Rash Illness, by Year, Kingdom of Saudi Arabia, 2013 – 2015

Year	Rubella	Febrile Rash illness	%	95% CI*	
				Lower	Upper
2013	66	1239	5.33	4.16	6.73
2014	23	832	2.76	1.80	4.08
2015	5	1122	0.45	0.17	0.98
Total	94	3193			

*CI = confidence interval

Table 3. Incidence of Confirmed Rubella by Year and Gender, Kingdom of Saudi Arabia, 2013 – 2015

Year	Male			Female			p-value
	Cases	IR°	95% CI*	Cases	IR°	95% CI*	
2013	34	0.20	0.14 – 0.28	32	0.25	0.17 - 0.35	0.40
2014	9	0.05	0.03- 0.095	14	0.11	0.06 - 0.17	0.10
2015	4	0.02	0.01 - 0.05	1	0.01	0.001 - 0.03	0.34
Total	47			47			

°IR = incidence rate per 100,000 population

*CI = confidence interval

Table 4. Percentage of Confirmed Rubella among Cases of Febrile Rash Illness, by Year and Gender, Kingdom of Saudi Arabia, 2013 – 2015

Year	Male			Female			p-value
	Cases	%	95% CI*	Cases	%	95% CI*	
2013	34	5.46	3.85- 7.53	32	5.48	3.82 – 7.63	0.99
2014	9	1.92	0.95- 3.50	14	3.90	2.223 - 6.14	0.098
2015	4	0.67	0.22- 1.58	1	0.19	0.017 - 0. 90	0.27
Total	47			47			

*CI = confidence interval

Table 5. Incidence of Confirmed Rubella by Year and Nationality, Kingdom of Saudi Arabia, 2013 – 2015

Year	Saudi			Non-Saudi			p-value value
	Cases	IR°	95% CI*	Cases	IR°	95% CI*	
2013	49	0.24	0.18 - 0.32	17	0.17	4.03 - 10.43	0.25
2014	15	0.07	0.04-0.12	8	0.08	1.96 - 7.82	0.82
2015	5	0.02	0.01 – 0.05	0	0	0.00- 0.02	0.28
Total	69			25			

°IR = incidence rate per 100,000 population

*CI = confidence interval

Table 6. Percentage of Confirmed Rubella among Cases of Febrile Rash Illness, by Year and Nationality, Kingdom of Saudi Arabia, 2013 – 2015

Year	Saudi			Non-Saudi			p-value
	Cases	%	95% CI*	Cases	%	95% CI*	
2013	49	5.02	3.76- 6.59	17	6.67	0.11 - 0.27	0.32
2014	15	2.36	1.38 - 3.79	8	4.15	0.04 - 0.14	0.21
2015	5	0.55	0.21 - 1.21	0	0	-0.001-1.16	0.03
Total	69			25			

*CI = confidence interval

Table 7. Descriptive Epidemiology of Confirmed Rubella Cases

Descriptive epidemiology	Number of Confirmed Rubella Cases Distributed by Years							
	2013	%	2014	%	2015	%	Total	%
Age group								
Less than 1 year	2	3.03	3	13.04	0	0.00	5	5.32
1 to 4 years	31	46.97	8	34.78	1	20.00	40	42.55
5 to 19 years	10	15.15	9	39.13	0	0.00	19	20.21
20 to 34 years	20	30.30	2	8.70	0	0.00	22	23.40
35 to 49 years	3	4.55	1	4.35	4	80.00	8	8.51
Gender								
Female	32	48.48	14	60.87	1	20.00	47	50.00
Male	34	51.52	9	39.13	4	80.00	47	50.00
Nationality								
Non-Saudi	17	25.76	8	34.78	0	0.00	25	26.60
Saudi	49	74.24	15	65.22	5	100.00	69	73.40
Grand Total	66	100	23	100	5	100.00	94	100

Table 8. Reported Cases of Rubella and Febrile rash illness by Year and Region, Kingdom of Saudi Arabia, 2013 – 2015

Regions	Confirmed rubella cases	%	Febrile rash illness	%
Makkah	32	34.04	881	27.59
Riyadh	24	25.53	872	27.31
Eastern	14	14.89	423	13.25
Al-medinah	7	7.45	185	5.79
Najran	7	7.45	174	5.45
Hail	2	2.13	126	3.95
Assir	0	0.00	111	3.48
Al-jouf	0	0.00	104	3.26
Jazan	0	0.00	83	2.60
Al-qasim	5	5.32	72	2.25
Northern	2	2.13	74	2.32
Tabouk	0	0.00	56	1.75
Al-baha	1	1.06	23	0.72
#N/A	0	0.00	9	0.28
Total	94	100.00	3193	100.00

 # N/A= the data not available

Table 9. Reported Cases of Confirmed Rubella, By Year and Vaccination Status, Kingdom of Saudi Arabia, 20013 – 2015

Vaccination status	2013	2014	2015	Grand Total	%
Not Eligible	2	3	0	5	5.32
Not Vaccinated	38	8	2	48	51.06
One MMR Dose	0	7	1	8	8.51
Two or more MMR Doses	0	1	0	1	1.06
Unknown	26	0	2	28	29.79
N/A	0	4	0	4	4.26
Grand Total	66	23	5	94	100.00

Table 10. Symptomatology of Rubella Cases (N=28), Kingdom of Saudi Arabia, 2014 – 2015

Signs & Symptoms	Number of cases	%
Fever	28	100.00
Rash	28	100.00
Cough	10	35.71
Conjunctivitis	5	17.86
Sore throat	14	50.00
Coryza	8	28.57
Koplike spot	4	14.29

Table 11. Descriptive Epidemiology for Confirmed Dual Infection (Rubella and Measles) Cases:

Descriptive Epidemiology	Confirmed Dual Infection Cases				
	2013	2014	2015	Grand Total	%
Age Groups					
Less than 1 year old	0	2	0	2	13.33
1 to 4 years old	2	4	0	6	40
5 to 19 years old	2	1	0	3	20
20 to 34 years old	2	0	0	2	13.33
35 to 49 years old	0	1	1	2	13.33
Gender					
Female	2	6	1	9	60
Male	4	2	0	6	40
Nationality					
Non-Saudi	2	3	0	5	33.33
Saudi	4	5	1	10	66.67
Regions					
Al-medinah	2	0	0	2	13.33
Eastern	1	3	0	4	26.67
Hail	0	0	1	1	6.67
Makkah	3	4	0	7	46.67
Riyadh	0	1	0	1	6.67
Vaccination status					
Not Eligible	0	2	0	2	13.33
Not Vaccinated	4	4	0	8	53.33
One MMR Dose	0	2	0	2	13.33
Unknown	2	0	1	3	20
Grand Total	6	8	1	15	100

Table 12. Descriptive Epidemiology for Febrile Rash Illness

Vaccination status	Cases of Febrile Rash Illness							
	2013	%	2014	%	2015	%	Total	%
Age group								
Less than 1 year old	27	2.18	123	14.78	219	19.52	369	11.56
1 to 4 years old	347	28.01	221	26.56	368	32.80	936	29.31
5 to 19 years old	197	15.90	287	34.50	294	26.20	778	24.37
20 to 34 years old	464	37.45	132	15.87	145	12.92	741	23.21
35 to 49 years old	87	7.02	53	6.37	80	7.13	220	6.89
Above 50 years old	10	0.81	13	1.56	15	1.34	38	1.19
#N/A	107	8.64	3	0.36	1	0.09	111	3.48
Gender								
Female	587	47.38	359	43.15	520	46.35	1466	45.91
Male	629	50.77	469	56.37	601	53.57	1699	53.21
#N/A	23	1.86	4	0.48	1	0.09	28	0.88
Nationality								
No nationality	0	0	0	0	1	0.09	1	0.03
Non-Saudi	255	20.58	193	23.2	212	18.89	660	20.67
Saudi	984	79.42	636	76.44	908	80.93	2528	79.17
#N/A	0	0	3	0.36	1	0.09	4	0.13
Grand Total	1239	100	832	100	1122	100	3193	100

 # N/A= the data not available

Figure 1. Reported Cases of Rubella, By Year and Reported Month, Kingdom of Saudi Arabia, 20013 – 2015

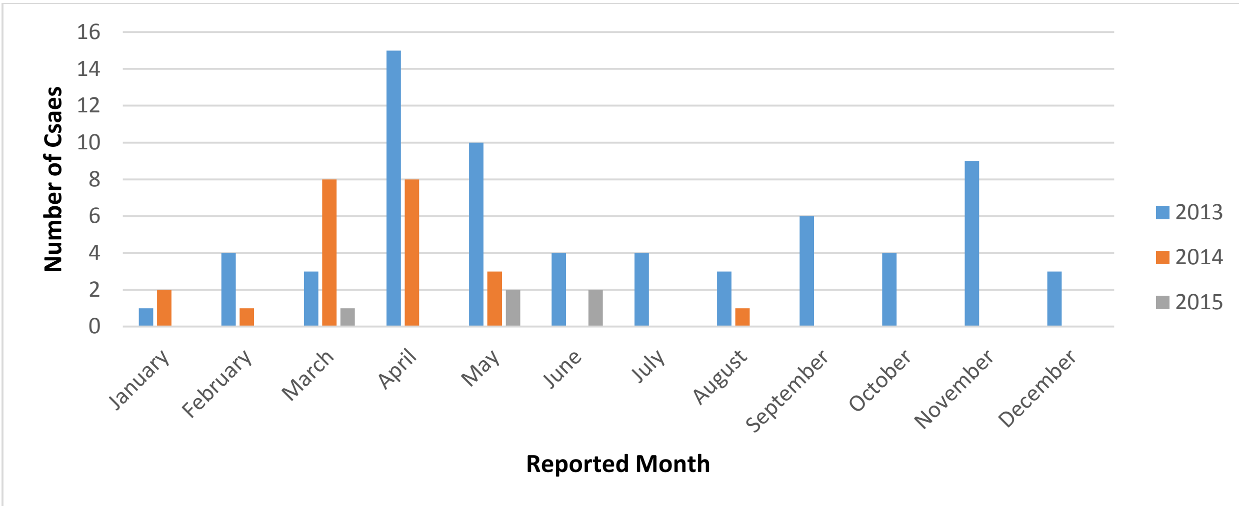


Figure 2. Reported Cases of Febrile Rash Illness by Year and Reported Month, Kingdom of Saudi Arabia, 20013 – 2015

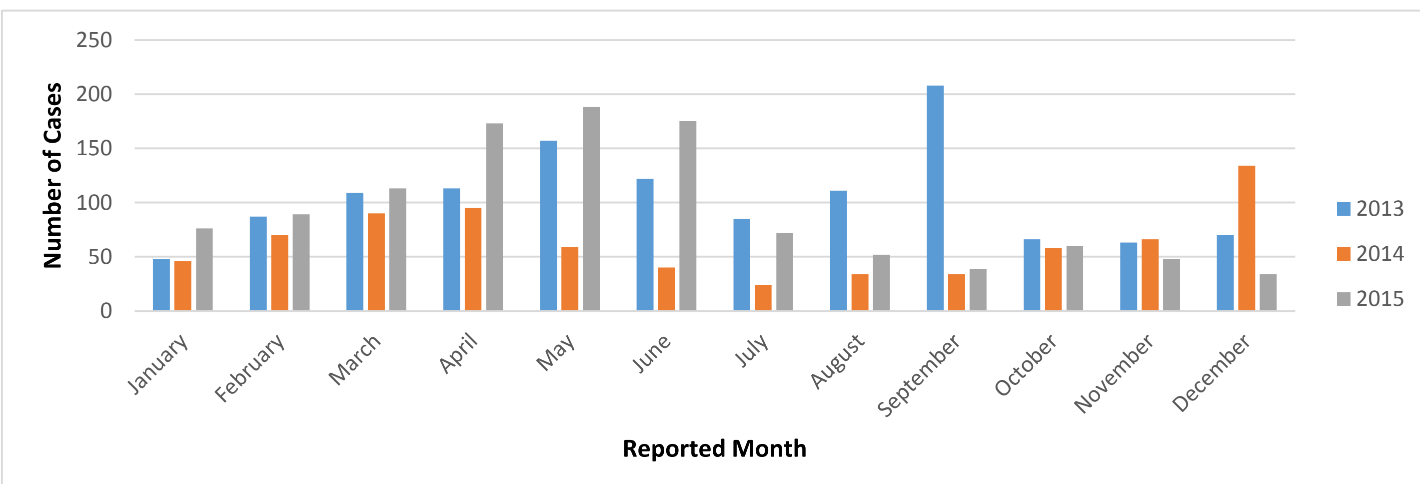
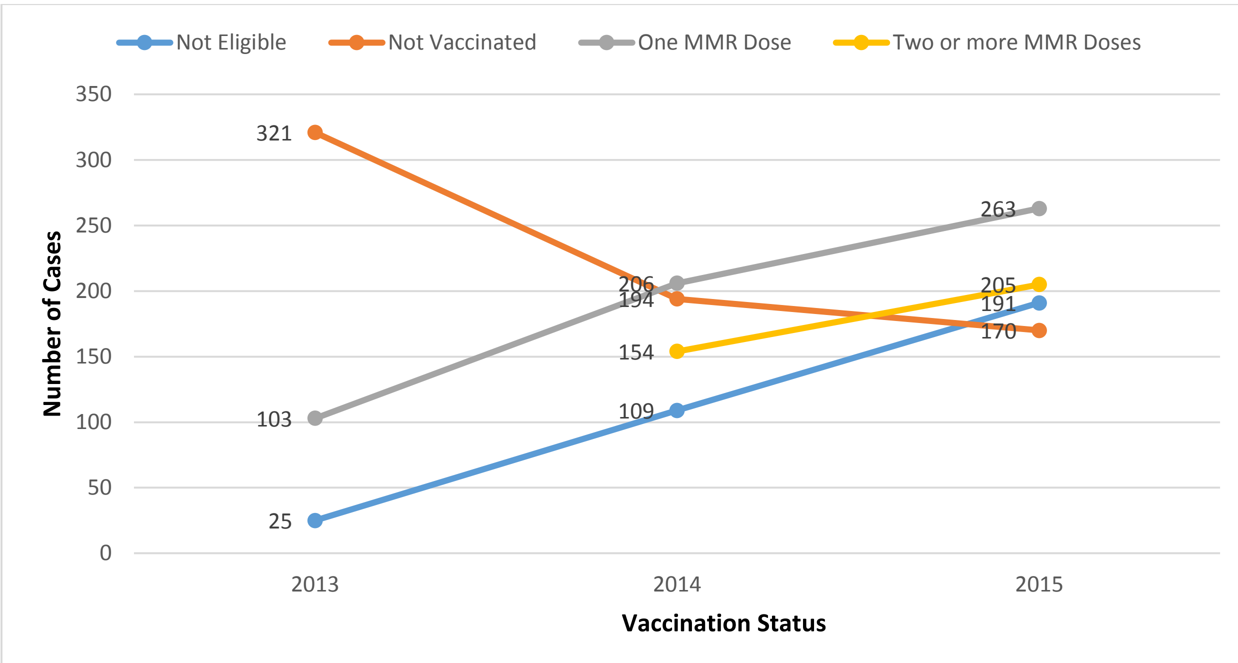


Figure 3. Reported Cases of Febrile Rash Illness, by Year and Vaccination Status, Kingdom of Saudi Arabia, 2013 – 2015



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