Effectiveness of combined Measles, Mumps and Rubella vaccine in Albania: An analysis based on health impact surveillance

Eftiola Pojani[1], Erida Nelaj[2], Artan Simaku[2], Alban Ylli[3]

[1]Catholic University "Our Lady of Good Counsel", Tirana, Albania;
[2]Institute of Public Health, Tirana, Albania;
[3]Faculty of Public Health, University of Medicine, Tirana, Albania.

Corresponding author: Eftiola Pojani;
Address: Rr. Dritan Hoxha, Tirana, Albania;
Telephone: 0035693938310; E-mail: eftiolapojani@yahoo.com

Abstract

Aim: In this paper we aim to provide an overview about the efficiency of combined measles-rubella (MR) and MMR (measles-mumps-rubella) vaccines in use in Albania during the last 15 years.
Methods: We used the Albanian epidemiological surveillance system on infectious diseases to estimate the health impact of the vaccination strategies in Albania, which has been historically using single and multi-antigen vaccines.
Results: Despite the limitations of our methodology that does not permit a firm conclusion about the effectiveness of the single antigen measles vaccine used in Albania before the year 2000, there seems to be a clear impact of the combined antigen vaccines MMR applied in the country since 2000. There is a clear time relation between the introduction of MR vaccine in 2001 and the virtual stop of circulation of measles in Albania. Few sporadic cases encountered in 2006-2007 remained isolated and no more cases were reported later. Similarly, parotitis cases, which have been reported by thousands per year in the 2000-2005 period, dropped immediately after 2006 and especially after 2007, where only 20-50 cases per year were reported in all Albanian districts.
Conclusion: It seems that, beyond any reasonable doubt, the dramatic decrease of the disease in the population was due to the block of virus circulation by effectively applying induced immunity among vaccinated children. This is equally true for measles and parotitis.

Keywords: effectiveness, immunization, impact, surveillance.

Introduction

Most of infectious diseases preventable-with-vaccination are transmitted through air, specifically known as measles, rubella, diphtheria, pertussis, epidemic parotitis (1).

Measles is a highly communicable disease caused by a morbillivirus and it may seriously threaten the health of the child because of complications such as pneumonia, croup, encephalitis and death. Prior to widespread immunization it was a common infection in childhood, so that more than 90% of the people had been infected by the age of 20 years.

Global measles deaths have decreased by 79% from an estimated 546,800 in 2000 to 114,900 in 2014 (2).

The measles vaccine has been in use for 50 years. WHO recommends immunization for all susceptible children and adults for whom measles vaccination is not contraindicated. Covering all children with two doses of measles vaccine, either alone, or in a measles-rubella (MR) or measles-mumps-rubella (MMR) combination, is considered as a standard for all national immunization programs (3).

In the pre-vaccination era, mumps constituted the main cause of viral encephalitis in many countries. By 2002, mumps vaccine was included in the routine immunization schedule of 121 countries. In countries where vaccination was not introduced, the incidence of mumps remains high, mostly affecting children aged 5-9 years (4).

Rubella, a mild febrile viral disease caused by *Rubella Virus*, is important for public health because of its ability to produce anomalies in the developing fetus. Congenital rubella syndrome (CRS) occurs in up to 90% of infants born to women who are infected with rubella during the first trimester of pregnancy. Vaccine is recommended for all susceptible non pregnant females without contraindications (4).

In Albania, measles vaccine has been in systematic use since 1971 as a single antigen (5). Because of the measles epidemic of 1970-71, an urgent mass vaccination of all birth cohorts 1956-1970 was carried out for the first time in Albania within three weeks throughout the country with the imported B55 attenuated live measles vaccine. In 1971, the routine mandatory vaccination against measles was introduced in the national immunization calendar for all new birth cohorts. Measles routine vaccination was based on the B55 attenuated live vaccine, that was first imported and then in 1977 started to be produced locally (5).

In 1992, the local production of B55 vaccine was interrupted, being substituted by the imported Schwarz measles vaccine in the routine mandatory vaccination. Since January 2001 Albania has introduced measles and rubella bi-vaccine in the calendar of mandatory immunization, giving a basal dose at 9th month of age and the booster dose at the age of 5 years. The mumps antigen was added to the National Immunization Program since the 1st of January 2005 introducing the combined tri-vaccine MMR, which is still in use today in Albania (5).

This vaccination strategy was implemented in the framework of the National Strategy for the elimination of measles and congenital rubella syndrome (5).

There are still some debates about the effectiveness of combined vaccine as compared to use of single vaccine (6-8).

In this paper we aim to provide facts about the effectiveness of combined MR and MMR vaccines in use in Albania during the last 15 years, based on data provided from the surveillance of vaccine controlled diseases in Albania.

Methods

We have used the Albanian epidemiological surveillance system on infectious diseases to estimate the health impact of the vaccination strategies in Albania, which as mentioned above, has been historically using single and multi-antigen vaccines.

The Albanian epidemiological surveillance system on infectious diseases has been and it continues to be a statutory one, the infectious diseases included in that system must be reported by law.

In 1997, the Department of Epidemiology (DE) of the Institute of Public Health in Albania initiated and carried out conspicuous quantitative and qualitative modifications of the statutory notification system thus compiling the new Major Disease-Based Epidemiological Surveillance System (MDBSS). The new highly improved reporting system was officially approved by the Albanian Ministry of Health and put into practice starting from January 1, 1998. In the compilation of the new statutory reporting system all of the attributes of an epidemiological surveillance system were taken into account such as flexibility, sensitivity and acceptability. The actual notification system contains 73 nosological entities of infection diseases presented in a standard official Form (named 14/Sh). The infection diseases are divided into three groups (namely A, B, C) in that Form according to the degree of their public health importance, based on the respective measuring parameters such as the magnitude of the problem, indices of disease severity, socio-economic impact and preventability. The aggregated data in the monthly 14/Sh Form are presented for each infectious diseases according to place (urban and rural), specific case definition (suspect and confirmed case), and age groups. The 14/Sh monthly Form of the actual reporting system is obligatorily by law to be accompanied by the Individual Forms for each Group, which contain detailed epidemiological information about the case-patient thus increasing, first of all, the specificity of the surveillance system and quantitatively and qualitatively enriching the system's epidemiological evidence (5).

Mandatory reporting system on Measles/Rubella Case-Based Surveillance represent in itself an addendum of the statutory reporting system of infectious diseases. These diseases are enlisted in the Group B of the 14/Sh Form and are of a rapid notification (within 1-3 days) from data sources to the local level and of a monthly notification from local level to the national one if their occurrence is represented as sporadic cases.

Data flow structure of the Alert System implies the weekly mandatory notification from the basic level (data sources) to the national one (DE of IPH) of the surveillance system through the local level (district epidemiological service).

Data handling includes data collection, check, aggregation and analysis in order to produce the weekly Alert Form, the monthly 14/Sh Form and yearly epidemiological report, which should be sent to the IPH.

Actually, all data sources are public. Anyhow, the private health services are by law under the mandatory notification, concerning the epidemiological surveillance of infectious diseases. We have used the surveillance data since year 2000 till the latest available year (2013, 2014) for all 36 districts of Albania (5).

The data are presented in a way that unfolds the impact on health differences before and after the introduction of the combined vaccine. Regarding parotitis, the available data belong to the years 2001 to 2013, helping us realize that the number of cases in the districts of Albania have decreased after the application of the vaccine (5).

The surveillance on birth defects in Albania since 2007 does not have the necessary specificity to identify cases with Congenital Rubella Syndrome (CRS) and we have limited our health impact analysis based only on measles and parotitis based surveillance. Due to the insufficiency of data, the study of rubella is not included.

Data were analyzed in Stata and Excel software.

Results

In Albania, Measles, from 1945 till 1955 had its usual endemic circulation among country population, with two epidemic peaks: epidemic of 1947-48 with 40,106 cases, and epidemic of 1954-55, spread all over the country, with 190,020 cases. In

1956, immediately after epidemic of 1954-55, a strategy of a total quarantine toward each eventual imported measles case was established throughout Albania. As a result of such strategy a total elimination of indigenous measles over a 15 year period (1956-1970) was achieved.

Measles epidemic of 1970-1971 started in November 1970 when the period of quarantine was accidentally interrupted. In 1971, the routine mandatory vaccination against measles was introduced in the national immunization calendar for all new birth cohorts. Measles routine vaccination was based on the B55 attenuated live vaccine that was first imported and then in 1977 started to be produced locally.

July 1971 marked the beginning of an 18 year period (1971-1989) of indigenous measles elimination in Albania, due to the primary prevention through the specific vaccine prophylaxis. Episodes of imported cases (1981-1984) were not able to support the survival of measles circulation among the population because of such levels of the total herd immunity. Following the 18 year period of measles elimination, a nation-wide measles epidemic took place (April 1989-March 1990), being distributed in all country districts, with an attack rate of 5,374 cases per 100,000 population, but with a low case fatality. In 1992, the local production of B55 vaccine was interrupted, being substituted by the imported Schwarz measles vaccine in the routine mandatory vaccination (5). The period 1992-2000 was characterized by measles circulation at sporadic levels with small and limited outbreaks, with an annual average of 700-800 reported cases and zeros deaths. The pediatric age groups (1-14 years old) showed the highest incidence rates, more than 80-85% of the total annual reported cases.

Table 1. Measles cases and incidences over the years in Albania

Measles	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
Cases (n)	662	18	0	0	0	0	68	22	0	0	0	0	0	0
Incidence	21.1	0.6	0	0	0	0	2.2	0.7	0	0	0	0	0	0

Since 2003, Albania had been classified as a measles free country until two epidemic outbreaks emerged in 2006 and 2007 mainly among Roma population in the districts of Elbasan, Saranda (2006) and Shkodra (2007). They were monitored and efficiently stopped due to the interference of immediate mass vaccination in these populations. Based on the studies conducted by genotyping in the laboratory of virology, it was proved that the epidemic emerged in Elbasan and Saranda had a single source, originally coming from Greece, while the one emerged in Shkodra district had its source in Italy. An immediate reduction of measles cases was noticed and for nearly 4 years Albania was considered "free" from measels (11). Through ALERT system, maculopapular rash cases are reported in epidemiology sector, but so far none has been confirmed to be measles.

Rubella

The average annual number of reported rubella cases over the period 1964-2001 is 9.6 cases, but there are even years with zero cases such as 1980 and 1981. The epidemic peaks were recorded over the period: 1969 with 3,676 reported cases, epidemic of 1985, the largest one, with 78,594 reported cases, and epidemic of 1994 with 3,432 reported cases. Age groups of 5-14 years old represent 60-70% of rubella cases, both in each epidemic peak. Meanwhile, older age groups (25-44 years old) are not exempted from rubella virus infection: they represent 1-2% of the total annual rubella reported cases over the period 1964-2001. There are not statistically significant differences of rubella incidence among country districts and incidence between urban or rural areas. The real weight of rubella infection in Albania is given by

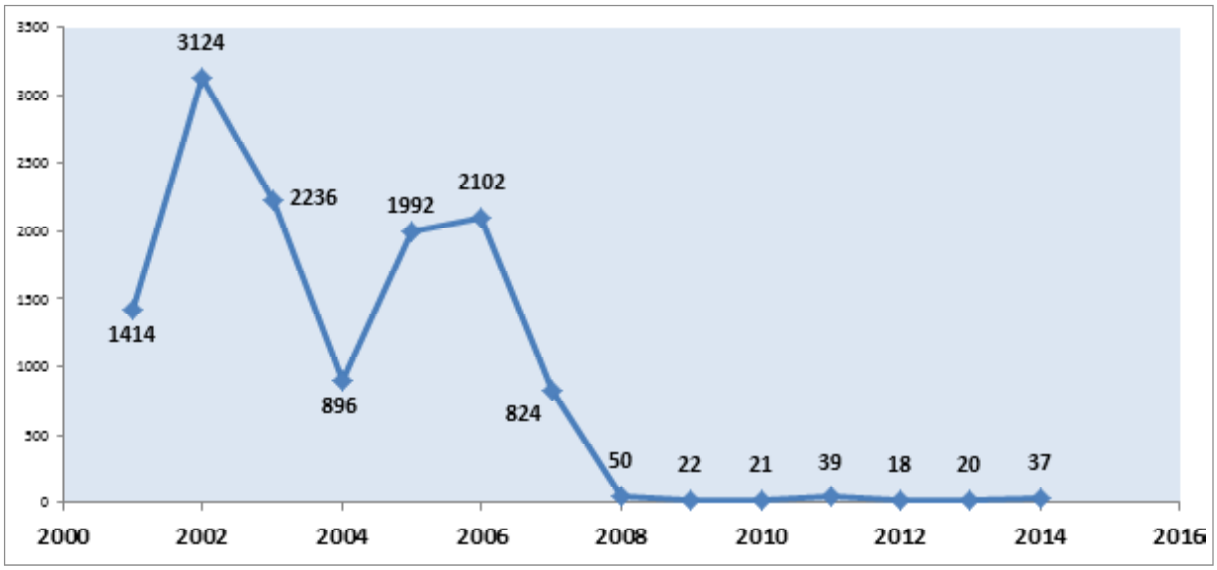
cross-sectional sero-epidemiological surveys, conducted in 1981, 1983, 1989 and 1995-1996 by the Institute of Public Health. The total rubella seroprevalence rate varies from 48% to 58% in inter-epidemic intervals, being increased up to 86-87% immediately after rubella epidemic circulation. Meanwhile, there are significant differences in age specific immune profiles, resulting to be: generally low from 10-30% at pre-puberty age groups, at puberty age increased to 30-70% and over 90% at post-puberty age groups. Such a strong relationship of rubella seropositivity levels with age essentially represents the specific feature of rubella epidemiology in Albania, quite contrary to other European countries during the pre-vaccine era.

Though there is not any evidence on Congenital Rubella Syndrome (CRS) occurrence in Albania yet, it might be evaluated as an annual expected number of around 70 cases. Furthermore, there is a significant pool of susceptible cases in puberty and post-puberty age groups just because of the above age specificity of rubella incidence, which overemphasizes the high risk of CRS in Albania. A mass vaccination (with measles-rubella bi-vaccine) of pediatric age was carried out in Albania in November 2000. On 1 January 2001 it was introduced in the calendar of mandatory immunization in Albania.

Results for the period after the introduction of MMR vaccine

A considerable (high) number of cases were noticed in the year 2002. More than 700 cases were reported to be encountered in our capital city in 2002. In 2003 the city of Shkodra counted about 400 cases, followed by a decrease in the number of cases in 2005 in Korca, Gjirokastra, Vlora and Shkodra. Referring to Figure 1, we can say that the peak with 3,124 cases was reached in 2002 followed by 2,236 cases in 2003 and 2,102 cases in the year 2006. It is obviously noticed that the situation remained constant starting from 2008 onwards.

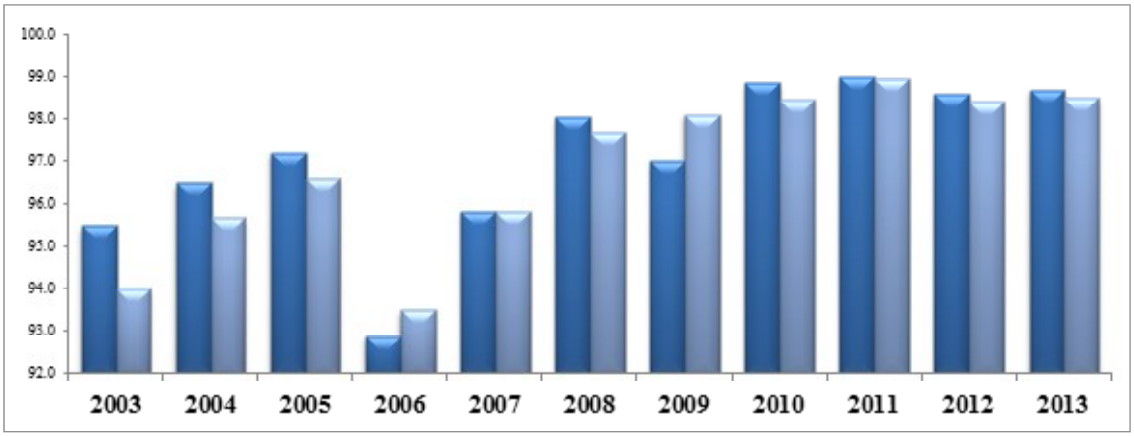
Figure 1. Distribution of parotitis cases over years



Considering these data, we noticed that from 2,000 verified cases encountered in 2006, the number of cases during the recent years varies from 20 to 30. The disease incidence has gradually decreased throughout Albania from the year 2006 onwards. Figure 2 presents cases that have been identified over the years in the largest districts of the country (9).

The situation after 2006 appears to have taken another trend and we notice a steady decline in the reported cases and, therefore, we conider that the combined MMR vaccine is effective in Albania (10).

Figure 2. Immunization coverage for the two doses of vaccine containing measles component (MR/MMR)



For the first dose of vaccine, the average coverage value is estimated to be around 98% which shows that the vaccination coverage is also high at the district level. Examination of Figure 2 and Figure 1 (which presents the distribution of the cases for parotid component over the years, from 3,124 cases in 2002 to 20-30 cases in 2014), indicates a steady decline in the reported cases and, therefore (9), we consider that the combined MMR vaccine is effective in Albania, despite some small geographic differences.

Discussion

The history of vaccination for measles, parotitis and rubella has been going through phases where different approaches have been applied. The period of full isolation was followed by massive vaccination of various single antigen vaccine against measles. Obvious health improvement has been noticed but nonetheless, the virus has been circulating in the limited groups of the population and has even caused (somehow mild) large-scale epidemics.

The situation may become problematic in cases when parents refuse to immunize their children, and if the number of refusals increases, our country may face measles epidemic as it has happened in the United States, England and France in the last years. Vaccination in Albania is still optional, i.e., parents themselves decide if they want to vaccinate their child. Their skepticism would endanger other children's life. So, the need to increase parents' awareness on vaccination becomes a necessity; they must never neglect the vaccination of their children as the current need in Albania is to maintain the highest vaccine coverage possible.

When measles is endemic, routine monthly reporting of aggregated data on clinical measles cases is recommended by district, age group and immunization status. In situations of low-incidence should be conducted a Case-based surveillance and every case should be reported and investigated immediately. Suspected measles outbreaks should be confirmed by conducting serology on the first 5-10 cases only (12).

In case of endemic mumps, it is recommended routine monthly reporting of aggregated data of clinical mumps cases by district. Only outbreaks (not each case) should be investigated. Suspected mumps outbreaks should be confirmed by con-

ducting laboratory investigation on 5-10 cases only. In specific situations, viral isolation can be attempted to differentiate meningitis cases that could be related to the wild virus, the vaccine strain or other factors (13).

Despite the limitations of our methodology that does not allow us to firmly conclude about the effectiveness of the single antigen measles vaccine used in Albania before the year 2000, there seem to be a clear impact of the combined antigen vaccines MMR applied in the country since that year. There is a clear time relation between the introduction of MR vaccine in 2001 and the virtual stop of circulation of measles in Albania. Few sporadic cases encountered in 2006-2007 remained isolated and no more cases are reported in the later years.

Similarly, parotitis cases which have been reported by thousands per year in the 2000-2005 period, dropped immediately after 2006 and especially after 2007, where only 20-50 cases per year were reported in all Albanian districts.

It seems that beyond any reasonable doubt, the reason for that dramatic decrease of the disease in population is the block of virus circulation by effectively applying induced immunity among vaccinated children. This is equally true for measles and parotitis as well.

For rubella the limits in methodology hindered us to prove the same fact.

Our analysis focused mostly on the effectiveness of vaccine among those undergoing routine appropriate immunization. Nevertheless, it is equally important to verify other components of a vaccination programme, such as vaccination coverage, clustering of problems in some large areas, cold chain quality, and the like. In our study, we were able to include some of them but not all. For the data related to vaccine coverage, some time correlation can be seen among the increase of the vaccination coverage during the two periods; 2003-2007 and afterwards. The only reported cases of measles in Albania belonged to that period (exactly the end of it) and practically the natural circulation of parotitis, despite its smaller scale, seemed to continue for two years after the introduction of the parotitis vaccine, and there were still some hundred cases in 2007.

In addition, we verified and proved that there might be some conditions that potentially affect the circulation of the virus of parotitis in Albania. To achieve the maximum effectiveness, the vaccination program should ensure the equality of the coverage among all populations. It seems that in Albania living in a region geographically positioned in a more western district or lower sea level altitude could increase the chances to be more exposed to parotitis. One of the reasons for that could be the higher density rate of the communities living in those areas and the increased possibility for contacts between infected sources and susceptible individuals. It should be noted that an effective vaccination programme must be accompanied by an effective public health surveillance of diseases to be controlled.

It is assumed that, while the ongoing vaccination programme based on MMR is achieving the objectives, it can be easily jeopardised by a lowering of vaccination coverage, especially in certain geographical areas.

Conflicts of interest: None declared.

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