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overview

Impact of vaccination on vaccine-preventable disease burden in Croatia

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Abstract

The epidemiology of vaccine-preventable diseases is a result of numerous factors, among which organized active immunization is one of the most important. Analysis of trends in disease incidence of vaccine-preventable diseases is an adequate way to provide evidence of impact of vaccination on disease burden.

In this manuscript, trends in vaccine-preventable diseases in Croatia are analyzed. Due to high vaccination coverage with safe and efficacious vaccines, some diseases like poliomyelitis and diphtheria have been eliminated in Croatia, while measles and rubella are at the point of elimination and burden of other vaccine-preventable diseases has been reduced significantly. Until recently, most of the vaccines used in the national immunization schedule have been produced by the Institute of Immunology, Zagreb, and the reduction of disease incidence is largely attributable to the Institute's vaccines. This especially refers to the Koprowski oral polio vaccine, measles, mumps, rubella and diphtheria, tetanus, pertussis vaccines.

INTRODUCTION

The epidemiology of vaccine-preventable diseases is a result of numerous factors, among which organized active immunization is one of the most important. Therefore, analysis of trends in disease incidence of vaccine-preventable diseases is an adequate way to provide evidence of impact of vaccination on disease burden. This especially applies to air-borne diseases whose incidence cannot be influenced by improved sanitation and living conditions. Some opponents of vaccination may argue that active immunization does not have a significant impact on disease burden because some food-borne illnesses as typhoid fever and hepatitis A are eliminated or have declined significantly regardless of vaccination due to access to safe drinking water, improved waste-water management, personal hygiene, control of food-handling processes, use of antibiotics and nutrition status of the population. However, none of these factors have any real impact on diseases transmitted by the respiratory route, so analysis of trends of measles, mumps, rubella and pertussis provides a direct measure of the value of immunization. For diseases which are mainly transmitted by faecal-oral mode, like poliomyelitis, improved sanitation and living conditions definitely do have an impact on disease burden, however, wide-scale immunization has proved to accelerate disease elimination significantly.

Thanks to availability of effective, safe and low-cost vaccines for some of the communicable diseases which represented significant health burden to the community in the pre-vaccine era and to wide-scale usage of vaccines, the morbidity of these diseases has been reduced significantly. This encouraged the international public health community to aim at global eradication and elimination of certain diseases. The World Health Organization (WHO) has set goals to eradicate poliomyelitis globally and eliminate measles and congenital rubella regionally. The time-frame for achieving these goals has had to be prolonged due to inadequate vaccine coverage in endemic countries. Global eradication of poliomyelitis was first anticipated to be achieved by year 2000, but has been postponed to year 2018 *(1, 2)*.

The Global Measles and Rubella Strategic Plan aims to achieve measles and rubella elimination in at least five WHO regions by 2020 *(3)*. Elimination of measles and congenital rubella has been set for 2010 in the European region *(4),* but had to be prolonged to 2015 due to inadequate vaccination coverage in many European countries which are still experiencing huge outbreaks of measles among unvaccinated persons *(5, 6)*.

Croatia has been fortunate to have a reliable vaccine producer, which assured access to affordable, efficacious and safe vaccines and a well organized immunization delivery system, which resulted in eradication of poliomyelitis and virtual elimination of rubella and measles.

The Institute of Immunology Zagreb (Institute) has been supplying the national immunization programme with the respective vaccines since the introduction of diphtheria vaccination in 1948, tetanus vaccination in 1955, pertussis vaccination in 1959, poliomyelitis vaccination in 1961, measles vaccination in 1968, rubella vaccination in 1975 and mumps vaccination in 1976. Other vaccines included in the childhood immunization programme (BCG, hepatitis B, Haemophilus influenzae type B and combination vaccines containing acellular pertussis) are produced by foreign manufacturers. In order assess the value of vaccines produced by the Institute of Immunology, an analysis of trends of targeted vaccine-preventable diseases is presented in this paper.

MATERIALS AND METHODS

Data on disease incidence in Croatia originate from routine infectious disease surveillance system. Reporting of communicable diseases is mandatory in Croatia according to the Act on Protection against Communicable Diseases *(7, 8)*. Since the list of diseases has been updated gradually, data on some diseases exist since the period between two world wars, while for others data are available for one, two or a few decades.

All health care providers who diagnose a communicable disease from the list of reportable diseases are obliged to report it on a standardized form to a local epidemiology unit, according to the place of residence of a patient. A local epidemiologist is responsible for conducting an epidemiological investigation following a report, intervention, if required, and runs a registry of communicable disease reports for the territory under his/her responsibility. By sending reports to the local epidemiologist, according to the patients' home address, duplications of reports are avoided. The local epidemiologist also sends the report to the county Institute of Public Health and to the Croatian National Institute of Public Health (CNIPH). The CNIPH receives 60 000 to 70 000 individual reports per year. At each level: local, county and national, the reports are analyzed on a daily basis and control measures implemented if needed.

Reports of adverse events following immunization are handled in a similar way, also based on the same law and respective bylaws. According to the Act on Protection against Communicable Diseases, healthcare providers who identify an adverse event following immunization should report it to the CNIPH and, according to the Act on medicines, adverse events should also be reported to the Croatian Agency for Medicines and Medical Products (CAMMP) (9). In reality, health-care workers (HCWs) usually report adverse events to the local epidemiologist or county Institute of Public Health and to the CNIPH or CAMMP. In order to make sure the CNIPH and CAMMP both receive and analyze the reports, a working group on adverse events following immunization, consisting of experts from the CNIPH and the CAMMP meets twice a month in order to exchange received reports and discuss each individual report.

Information on vaccination coverage is also regulated by the Act on Protection against Communicable Diseases and respective bylaws and is collected and analyzed annually at all levels. The most important bylaw, which regulates reporting on immunization coverage, is the Ordinance on the National Immunization Schedule for Croatia, which is issued by the minister of health annually.

Therefore, all prerequisites for evaluation of the national immunization programme are fulfilled: disease surveillance, adverse events following immunization surveillance and vaccination coverage monitoring.

The analyses presented in this paper are based on the data collected and compiled by the Croatian National institute of Public Health.

RESULTS

Diphtheria

Vaccination against diphtheria was introduced into the mandatory childhood vaccination schedule in 1948. In the first years following the introduction of vaccination, no effect on disease incidence was observed due to unsatisfactory vaccination coverage. A few years after introduction, due to improved vaccination coverage, the incidence of disease declined steadily until the seventies, with the last case of diphtheria recorded in Croatia in 1974 (Figure 1.). The vaccine produced by the Institute was used for primary vaccination and boosters throughout childhood and school age, until the eighth grade of

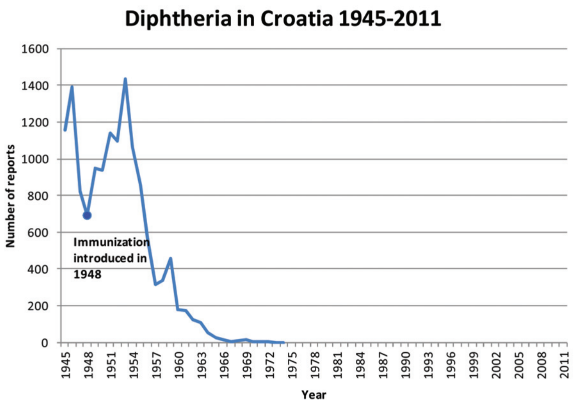

Figure 1. *Incidence of diphtheria in Croatia in the 1945-2011 period.*

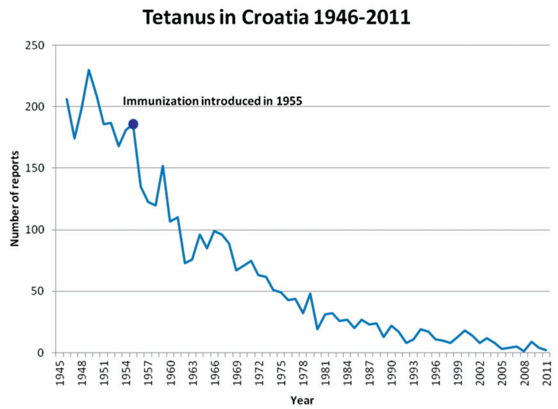

Figure 2. *Incidence of tetanus in Croatia in the 1946-2011 period.*

elementary school up to 1995. Following large outbreaks of diphtheria in Eastern Europe during the 1990s, an additional booster dose was added into the national immunization schedule for 18-year old children in 1995. Due to high immunization coverage, Croatia was not affected by the resurgence of diphtheria in the 1990s. Additionally, a seroprevalence study in the Croatian population born between 1934 and 1974 was performed in 1994 *(10)*. All study participants (N=223) had anti-diphtheria toxin antibodies above the minimum protective level of 0.01 IU/ml measured by enzyme-linked immunosorbent assay (ELISA) and neutralization test (NT). Interestingly, persons born between 1964 and 1974 had highest geometric mean titres (GMT) of antibodies and the GMT declined towards older age groups, indicating waning immunity. The results of this study also indicate that immunity conferred by the vaccine used in Croatia is not inferior to immunity conferred by natural contact with the bacteria, since the age group with the highest GMTs had a much lower chance to be in contact with C. diphtheriae than the older age groups. This same vaccine is still used in Croatia for diphtheria booster immunization at seven, fourteen and eighteen years of age. The vaccine has shown an excellent safety profile, with local reactions at the injection site being the majority of reported adverse events following immunization.

Tetanus

Vaccination against tetanus was introduced into the vaccination schedule in 1955. From the beginning of tetanus immunization, combination vaccine produced by the Institute and consisting of diphtheria and tetanus toxoids were used in infants and pre-school children. Pertussis was later added to the combination vaccine for infants and pre-school children. For school-aged children, a tetanus-diphtheria combination vaccine with a lesser amount of diphtheria toxoid is used.

The incidence of tetanus in Croatia is presented in Figure 2.

Besides reduction in tetanus incidence, a significant shift of morbidity to older age groups occurred. At the time before introduction of the vaccine into the immunization programme during the 1940s and 1950s, tetanus patients were predominantly working-age men, while in the past ten years virtually all patients were unvaccinated women older than 60 years. In order to address older persons who were born before the introduction of tetanus vaccination, immunization of 60-year old persons was added to the immunization programme in 2002.

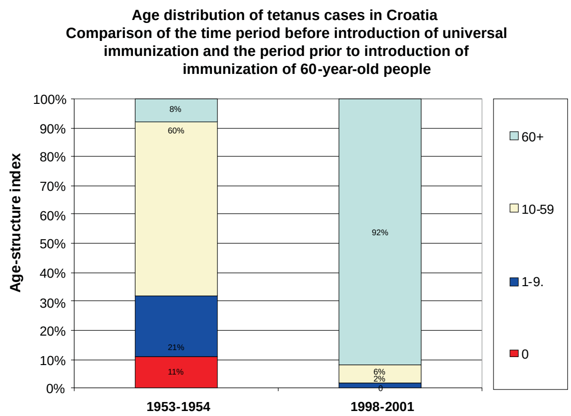

Figure 3. *Age distribution of tetanus cases in Croatia, comparison of the 1953-1954 period with the 1998-2001 period.*

Figure 3 illustrates the significant change in the age structure of tetanus patients in Croatia, which was the basis for the decision to add immunization of 60-year old persons.

Neonatal tetanus has been eliminated due to high vaccination coverage among women of child-bearing age.

Combined diphtheria-tetanus vaccine produced by the Institute is still used in Croatia for immunization of school-aged children.

The vaccine has shown an excellent safety profile, with local reactions at the injection site being the majority of reported adverse events following immunization.

Pertussis

Following the introduction of pertussis vaccine into immunization programme, a sharp and steady decline in pertussis incidence was observed, as shown in Figure 4.

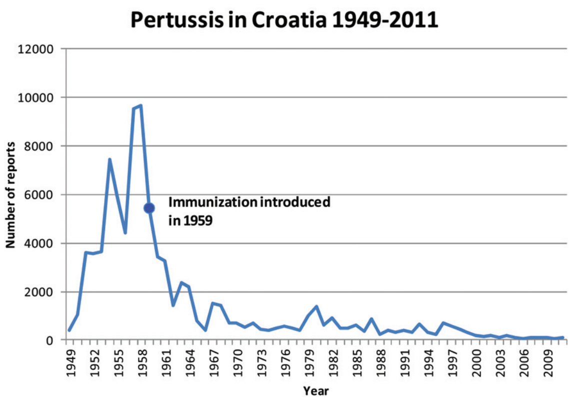

Figure 4. *Incidence of pertussis in the Croatia 1949-2011 period.*

The vaccine responsible for this high impact on disease incidence is combined whole-cell diphtheria-tetanus-pertussis vaccine produced by the Institute. The incidence of pertussis declined from an annual average of 5000 cases at the time of vaccine introduction to less than 100 casses per year in the last decade. Most pertussis cases in the last decade are infants who are too young to be protected by vaccination.

In 2008, due to adding additional injectable vaccines to the pre-school immunization schedule (adding hepatitis B vaccination to infants and switching from OPV to IPV), the Institute's DTP vaccine was replaced by a combination vaccine containing diphtheria, tetanus, acellular pertussis, inactivated polio and Hib (DTP-IPV--Hib) in order to reduce the number of injectins in infancy and early childhood. This was a compromise in which a possibly less efficacious pertussis vaccine was introduced in order to ensure compliance with the immunization schedule. Four years of use of the acellular pertussis vaccine are still a too short period to evaluate the impact of switching from the highly efficacious whole--cell pertussis vaccine to acellular pertussis vaccine.

Adverse events attributable to the whole-cell pertussis component of the Institute's DTP vaccine have been reported rarely, mostly being inconsolable crying, while for the majority of reported adverse events (induration, redness and swelling at the injection site) it is not possible to discern to which component of the combination vaccine the local reaction is attributable. There have been no reports of long term neurological consequences following administration of this DTP vaccine in Croatia.

Poliomyelitis

In 1961, another highly efficacious vaccine produced by the Institute was added to the immunization programme in Croatia. The Koprowski live polio vaccine (OPV) was introduced through a wide range immunization campaign, during which the entire Croatian population between three months and 20 years received OPV in two rounds of vaccination during 1961–1962. After the campaign, immunization of infants with boosters in pre-school and school-aged childred continued on a routine basis. The vaccine produced by the Institute was used until 1983 when it was replaced by Sabin OPV. In 2008 OPV was replaced by inactivated polio vaccine (IPV). Annually, there were tens to few hundreds of cases reported before the introduction of vaccination. Immediately after the mass vaccination campaign, the number of poliomyelitis cases dropped below ten per year, as illustrated in Figure 5. The last case of poliomyelitis in Croatia was reported in 1989, following a ten-year period with an average annual incidence below one case per year. Therefore, the elimination of poliomyelitis was achieved with the Institute's vaccine. After the elimination of poliomyelitis, additional enhanced acute flaccid paralysis surveillance and environmental surveillance have taken place in order to document eradication of poliovirus from the population. In 2002, the European region of WHO was declared polio-free. On this occasion, a small number of individuals, experts and professionals who were recognized as most deserving for this success received certificates from WHO for dedicated work on polio eradication and contribution to the elimination of polio from the European region. One of the four recipients in Croatia who also received brass polio eradication pins for exceptional contribution was Drago Ikić, full member of the Croatian Academy of Sciences and Arts, involved in the development and testing of the Koprowski OPV produced by the Institute of Immunology, Zagreb.

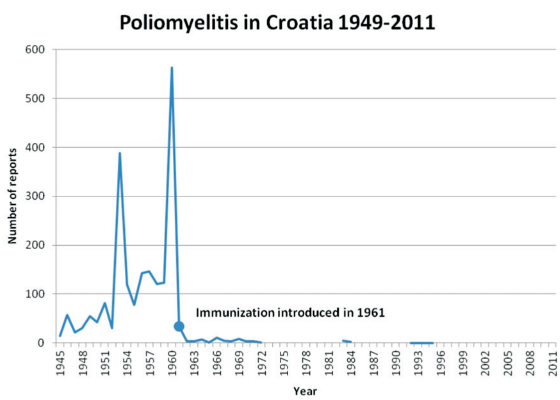

Figure 5. *Incidence of poliomyelitis in Croatia in the 1945-2011 period.*

Measles

Measles vaccine, produced from the further attenuated Edmonston-Zagreb strain by the Institute of Immunology was introduced into the immunization programme in 1968. In the beginning it was used as a monovalent measles vaccine, for the first and second dose. In 1976 a trivalent measles-mumps-rubella vaccine produced by the Institute replaced the monovalent vaccine for the first dose, and since 1994 trivalent vaccine was used also for the second dose. Due to adverse events caused by the mumps component of MMR, which occurred after the first dose of vaccine, this vaccine was replaced for the first dose by one of another producer in 2009. In 2011 this vaccine was replaced by another for the second dose, due

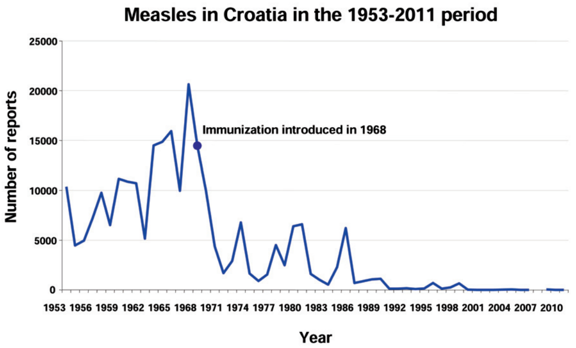

Figure 6. *Incidence of measles in in the Croatia 1953-2011 period.*

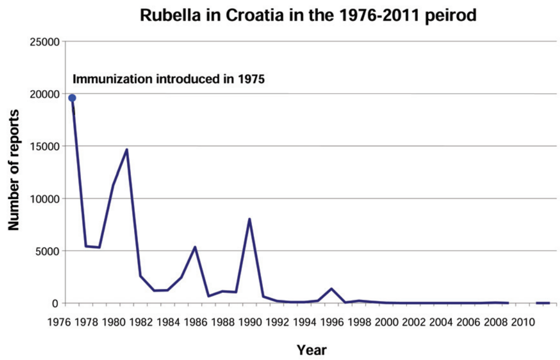

Figure 7. *Incidence of rubella in the Croatia 1976-2011 period.*

to discontinuation of its production. The results of four decades of using the Edmonston-Zagreb measles strain in Croatia are illustrated in Figure 6. Immediately after the introduction of measles vaccine into the immunization programme, the incidence declined to a range of 1000 to 7000 cases per year, compared to a range of 6000 to 16000 cases per year prior to vacccine introduction, and the interval between peak incidence years increased. With improved vaccination coverage during the 1990s, measles incidence further declined and never exceeded hundred cases per year since 1999. Actually, during the last decade only sporadic imported cases occurred, except for three small outbreaks involving mostly unvaccinated adults which followed importation of measles in years 2003/2004, 2008 and 2011 with 73, 51 and 12 cases involved, respectively. In the early years of measles vaccination, numerous field trials and observational studies confirmed the immunogenicity, effectiveness and safety of the Edmonston-Zagreb measles vaccine *(11, 12, 13, 14, 15, 16)*.

Based on the fact that the three small outbreaks in the last decade were easily controlled and that in the years between the outbreaks we did not see indigenous cases of measles, we may say that the use of Edmonston-Zagreb based measles vaccine resulted in elimination of measles in Croatia. The vaccine has shown to have a very good safety profile, with only a few adverse events reported annually which are likely to be attributed to the measles component of the MMR vaccine (e.g. morbilliform rash, purpura)

Rubella

Rubella vaccination was added to the childhood immunization programme in 1975, administered with the measles vaccine at the age of 12 months for all children and at the age of 14 as a monovalent vaccine only for girls. The following year, in 1976, it was given as part of an MMR combination vaccine at the age of 12 months, while it wasn't before 1994 that it was decided to give a second dose of rubella vaccine as part of combined MMR to all children, not only girls. Throughout the entire period, RA27/3 strain, produced by the Institute, has been used. More than 35 years of universal immunization resulted in virtual elimination of rubella in Croatia as illustrated in Figure 7.

The incidence of rubella decreased from several thousand cases at the time of vaccine introduction to sporadic imported cases in the last decade, with less than ten reports per year, with only one exception: a small outbreak of rubella among unvaccinated adolescents in Dubrovnik during 2007 with 39 cases.

Adverse events attributable to the rubella component of combined MMR vaccine (e.g. rubelliform rash, arthralgia) have been reported sporadically.

Mumps

Mumps vaccine, produced from the futher attenuated Leningrad-Zagreb strain was introduced into the immunization programme in 1976 as part of the trivalent MMR vaccine at the age of 12 months. In 1994 a second dose was added to the schedule at the age of six years. Although a significant success has been achieved in reducing the incidence of mumps, the reduction is slightly less remarkable than in the case of measles and rubella. In fact, epidemiological situation regarding mumps is similar to the one we had with measles and rubella at the turn of the century, just before the elimination phase. During the last decade, we had fourty to hundred-fifty indigenous mumps cases annually, compared to thousands of cases at the time of vaccine introduction, which is illustrated in Figure 8. The safety issue of this vaccine has been a matter of controversy in the last fifteen years. The mumps component of the combined MMR vaccine was responsible for tens of vaccine associated cases of parotitis annually and ten to twenty cases of aseptic meningitis. Due to the relatively mild symptomatology of both adverse events, it was acceptable to use this vaccine at the time of high incidence of mumps in the community. However, in the last decade, the incidence of vaccine associated mumps outnumbered the cases of naturally acquired mumps in some years. Regardless of the mentioned safety issues, the vaccine was not replaced in the immunization programme until a new adverse event was recognized. In late 2007 and during 2008, there were more than twenty reports of transmission of the vaccine virus to those in contact with the vaccinated, resulting in illness among the contacts. All instances of

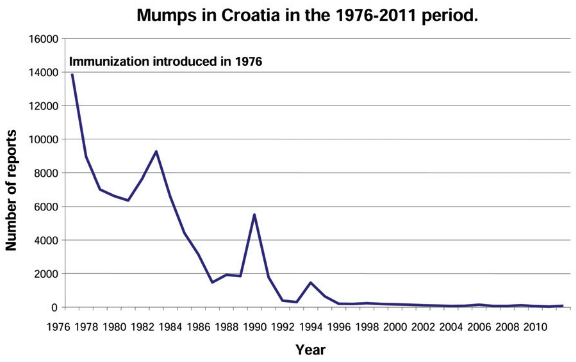

Figure 8. *Incidence of mumps in Croatia in the 1976-2011 period.*

transmission to contacts occurred after administration of the first dose of MMR vaccine, not after the second dose. For this reason, the MMR vaccine produced by the Institute was replaced by one of another producer for the first dose in the schedule in 2009. In 2011, Institute's MMR was replaced by another vaccine for the second dose as well, since the Institute discontinued its production.

DISCUSSION

Although the effect of vaccination can be measured in various ways, the impact on disease burden is definitely the most useful measure of vaccine effectiveness.

Comparing average disease incidence in the five-year period prior to vaccine introduction or immediately afterwards, depending on availability of data, and in the last five-year period we can easily calculate the reduction of disease incidence. Table 1 shows the reduction of disease burden expressed as a rate.

The table clearly shows a remarkable reduction in disease burden of vaccine-preventable disease. However, in order to clarify if this reduction of disease burden is a consequence of immunization or some other factors, it is best to compare the incidence trend of a vaccine preventable disease with the incidence trend of another disease with similar transmission patterns against which vaccination is not performed or available, provided that data on both diseases are collected through the same information system and in the same manner.

A good example for comparison are measles and chickenpox, two viral diseases with a high basic reproductive index, both spread by the same respiratory route, to which susceptibility is universal in an non-immune population. Vaccination against measles with two doses is mandatory since 1968 and vaccination coverage has reached rates higher than 95%, while vaccination against chickenpox is not included in the immunization schedule, has not been widely accepted as facultative vaccination and the coverage in children is estimated to be lower than 1%.

Figure 9. illustrates incidence trends of measles and chickenpox in Croatia since the time when reporting of these diseases has become mandatory.

A five-year moving average is added to the figure in order to smoothen the lines that illustrate the incidence of both diseases, and the y-axis scale is logarithmic in order to better show the dynamics (speed) of the change in incidence.

It is obvious from Figure 9 that a significant and rapid decrease in measles incidence followed the introduction of vaccination, while the existing, but much slower decrease in chickenpox incidence would need hundreds of years with this trend to reach the level measles have reached in some thirty years.

Similarly, if we compare the speed of reduction in poliomyelitis incidence with hepatitis A incidence, two

TABLE 1

Reduction of vaccine-preventable disease burden in Croatia.

Disease	Average annual incidence		Reduction of incidence (%)
	Five-year period prior to/at the time of vaccine introduction	Recent five-year period (2007–2011)	
Diphtheria	1 133	0	100
Tetanus	186	4	98
Pertussis	7 393	95	99
Poliomyelitis	219	0	100
Measles	15 183	14	>99
Rubella	11 248	8	>99
Mumps	8 569	53	99
Tuberculosis	13 785	862	94
Hepatitis B (acute) (1996-1998 / 2009-2011)	224	98	56
Invasive Hib disease (meningitis and sepsis) (1999–2001 / 2009–2011)	18	1	94

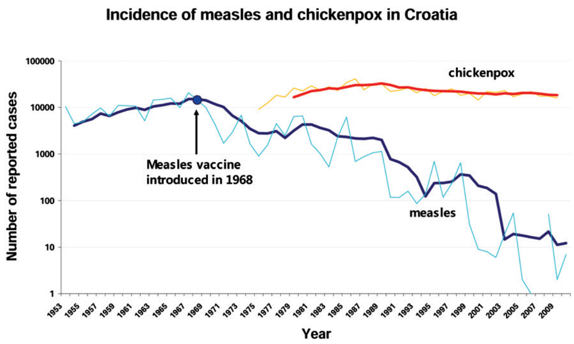

Figure 9. *Incidence trends of measles and chickenpox in Croatia.*

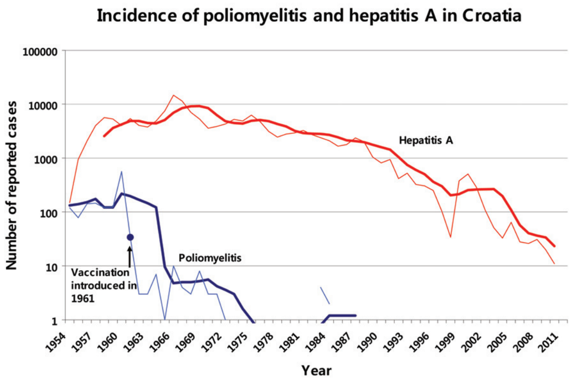

Figure 10. *Incidence trends of poliomyelitis and hepatitis A in Croatia.*

diseases with a comparable mode of transmission, as illustrated in Figure 10, it is clear that the rate of disease reduction is much faster in case of poliomyelitis.

Similarly to the previous figure, five-year moving averages of poliomyelitis and hepatitis A incidence are added in Figure 10, in order to smoothen the trend line. If only improved sanitation, personal hygiene, and living conditions were responsible for the elimination of poliomyelitis, as they are for control of hepatitis A, the rate of reduction would be similar for both diseases and the trend lines should be more or less parallel. It is obvious that the trend line of poliomyelitis is steeper than the one of hepatitis A, indicating that immunization accelerated the reduction of incidence.

Based on these analyses of incidence trends of vaccine-preventable diseases, it is quite reasonable to conclude that using the Institute's vaccines and maintaining high vaccination coverage in the national immunization schedule resulted in great reduction of disease burden in Croatia.

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