VIRAL IMMUNOLOGY
Volume 31, Number 10, 2018
Mary Ann Liebert, Inc.
Pp. 695–707
DOI: 10.1089/vim.2018.0054

Contribution of Vaccination to the Reduction of Infectious Mortality in Ukraine in the Second Half of the 20th and Early 21st Century: A Comparative Population-Based Study of the Dynamics and Structure of Infectious Mortality and Incidence

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Abstract

Our work presents an epidemiological analysis of the dynamics and structure of the annual indicators such as Cumulative Incidence, Mortality Rate (MR), and Case Fatality Rate for infections preventable by vaccines (vaccine-preventable infections–VPIs) in Ukraine between 1944 and 2015 compared to the same indicators for infections not preventable by vaccines (nonvaccine-preventable infections–non-VPIs). In 1965, the proportion of all infectious diseases in the context of mortality (7.47%), and especially of VPI (3.77%), including those registered among children aged 0–14 years (2.12%), testifies to the low profile of infectious diseases by the time of routine vaccination introduction. The analyses of these particular data are important with respect to the role of vaccination programs in reducing not only the total infectious mortality but also mortality related to VPIs in the twentieth century. Interestingly, in Ukraine between 1965 and 2015, similar rates of mortality reduction were observed in both the total population (1.6–2.6 times) and in children under 14 (15.2–20.4 times) for both VPIs and non-VPIs. During the 1944–2015 period in Ukraine, the reduction of MR of VPI (tuberculosis, diphtheria, tetanus, pertussis, poliomyelitis, measles, and hepatitis B) varied greatly, ranging from 40.5 times (tetanus) to 1,061.1 times (measles), but in general, the reduction incidence rate of VPI was significantly lower ranging from 42.4 times (measles) to 471.1 times (diphtheria). The ratio of incidence and mortality reduction in percent shows the contribution of vaccination to the mortality reduction for various infections during 1944–2015. This ratio ranged from 0% (tuberculosis) to 84.9% (tetanus), provided that the reduction of the VPI incidence 100% depends on vaccine effects. Thus, we can assume that the observed reduction in mortality for some VPIs was, in part, caused by factors not associated with vaccines.

Keywords: vaccination, infections, mortality, incidence

Background

Over the past 100 years, there has been a significant increase in life expectancy and a significantly lower proportion of deaths caused by infectious diseases in North America and Europe (2). The ''Theory of epidemiological transition'' links these trends with the transition from the ''epoch of plague and hunger,'' when infectious diseases were the predominant cause of death, especially in the preadolescent population, to the current ''era of degenerative and technology-related diseases,'' when mortality due to chronic diseases predominates (19,23). The Global Burden of Disease study conducted by the World Health Organization (WHO) estimates that infectious diseases currently represent only 4.2% of all disability-adjusted life years lost in countries presenting developed market economies such as the United States, while chronic and neoplastic diseases account for 81.0% (22).

In the United States, vaccination programs have greatly contributed to the elimination of many infectious diseases and have significantly reduced the incidence of other

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diseases. Vaccination campaigns in the United States targeting poliomyelitis, measles, and rubella viruses have effectively eliminated these diseases from North America. The more than 90% reduction in the number of reported infections and the almost complete prevention of fatalities caused by diseases preventable by vaccines recommended before 1980 have been accomplished for diphtheria, mumps, pertussis, and tetanus. The power and effectiveness of vaccination is exemplified by the global eradication of smallpox accomplished in 1977 following an intense and internationally coordinated vaccination campaign (28). A similar trend in the reduction in infectious disease incidence and associated mortality as described above was also observed in countries with a lower level of development. Despite availability of effective vaccines, as demonstrated by the ongoing outbreak of measles in Europe that has resulted in over 41,000 children being infected, with 47 deaths in the first 6 months of 2018 (25,27) and reports of over 5,000 cases and 68 deaths in the Americas (26), this long-term study for Ukraine is especially relevant.

Some authors hypothesize that vaccination is associated with nonspecific effects on mortality (20). For example, in the 1980s, the introduction of measles vaccination in some African communities and Bangladesh was accompanied by the significantly greater reduction in total child mortality than could be attributed to measles deaths (1,18). Such a coincidence of the decline in total mortality and the introduction of measles vaccination could, however, reflect a simple coincidence in time when multiple factors are changing.

In addition to vaccination, other factors likely contributed to the reduced incidence of fatal infectious diseases. These factors include improvements in sanitary and hygienic conditions, nutrition, labor legislation, medical care, the introduction of epidemiological surveillance, changing demographics, availability of electricity, chlorination of water, refrigeration and preservation of food, and pasteurization.

Although it is generally accepted that vaccines are a major contributor for the observed reduction in some cases of infection-related mortality, data to support this conclusion have not adequately been fully evaluated. Our access to mortality data for Ukraine with a population of approximately 52 million people provided an excellent and unprecedented opportunity to identify the contribution of vaccines toward changing patterns in the causes of death over a long period (1944–2015). Our data contain the most complete information concerning the incidence (Cumulative Incidence–CI), mortality (Mortality Rate–MR), and lethality (Case Fatality Rate–CFR) of the total and child populations of Ukraine for seven vaccine-preventable infectious diseases (tuberculosis, diphtheria, tetanus, pertussis, poliomyelitis, measles, and hepatitis B). Our data also contain information on the total and infectious mortality and incidence of the Ukrainian population. An important result of this research was the development of an algorithm for calculating the proportion (percentage) or quantitative impact (contribution) of vaccines among other causes of infectious mortality reduction. This algorithm is based on the logical, epidemiological, and mathematical relationship of the reduction rate in terms of the annual CI, MR, and CFR.

Materials and Methods

The basic data on the annual case numbers of deaths from infectious diseases in Ukraine before 2000 were extracted from several article sources (3,21,29). The data on the annual case numbers of deaths from infectious diseases in Ukraine for the 2001–2015 period were extracted from the C-8 statistical form ''Distribution of deceased persons by sex, age groups, and causes of death,'' which was provided by the State Institution ''Ukrainian Center for Disease Control and Monitoring of the Ministry of Health of Ukraine.''

The data on the annual case numbers of infectious diseases in Ukraine before 2009 were extracted from article sources (3,6–16,24,29). The data on the annual case numbers of infectious diseases in Ukraine for the 2010–2015 period were extracted from the statistical form No. 2 (annual) of the Ministry of Health of Ukraine ''Report on particular infections and parasitic diseases.'' Some of the data used are not fully available for public free access, although the data on mortality and morbidity in Ukraine for some periods are deposited in WHO electronic databases (5,30).

The data on immunization coverage in Ukraine before 1972 were extracted from the article source (3). Some data on immunization coverage in Ukraine from 1981 to 2015 were extracted from the WHO electronic database (5).

For the convenience of data analysis, we divided the entire time period under study into four time periods: 1944–1964, 1965–1991, 1992–2005, and 2006–2015. 1944–1964 were the last decades of the prevaccination period, but a gradual introduction of routine vaccination against tuberculosis, diphtheria, tetanus, pertussis, and poliomyelitis was initiated in different years of this period. 1965–1991 were the years of economic growth, formation, and functioning of sufficiently effective vaccination programs. In 1992–2005, there was a sharp decline in the economy and a deterioration in living standards, which were accompanied by the significant increase in rates of total population deaths from tuberculosis and other infections. The 2006–2015 period was characterized by a decline in economic growth that is yet to recover to reach even the level of 1991.

In this study, our goal was to determine the proportion (percentage) or quantitative impact (contribution) of vaccines among other causes of vaccine-preventable infection (VPI) mortality reduction. The design of our study is a comparative retrospective population-based study of the annual values of the epidemiological indicators such as CI, MR, and CFR for VPI and non-VPI. Perhaps, comparison of mortality dynamics for VPI and non-VPI indirectly allows determining the proportion (percentage) of the vaccine effect on mortality.

First, we arranged data on vaccine coverage in Ukraine for four (or three) time periods and built discontinuous time series of their annual CI, MR, and CFR.

For each period, the minimum, maximum, and average values (arithmetic mean) of the annual epidemiological indicators of vaccination coverage, incidence, and mortality were calculated. The CFR for each infection and for each period dividing the total number of deceased persons by the number of the disease cases for the corresponding period and then multiplying this quotient by 100% was then calculated. Finally, the ratio of the mean values for each epidemiological indicator as a quotient of dividing the average of the first period by the average of the last period was calculated. Based on these data and calculations, we determined the fold reduction in incidence, mortality, and lethality for each infectious disease in Ukraine for the periods of 1944–2015 or 1965–2015. We also determined the reduction in MR for VPI and non-VPI in Ukraine for 1991 and 2015 compared to 1965. The year of reaching 80–90% of vaccination coverage for tuberculosis, diphtheria, tetanus, pertussis, and poliomyelitis is 1965. The year when Ukraine gained independence and state sovereignty with good immunization coverage is 1991 (Table 1). The last year of the study with low immunization coverage was 2015 (Table 1).

In the most general sense, the incidence of an infectious disease is a complex biological and stochastic event that involves interactions between many natural and social factors. The risk (or probability) associated with disease incidence is equal to the product of the risks of two simple events, assuming that they occur simultaneously. These risk factors or the necessary conditions to initiate an infectious disease outbreak include specific population susceptibility and the possibility of transmission or infection by a specific infectious agent. Thus, the incidence risk is equal to the product of the susceptibility risk and the risk of transmission of the infectious agent.

The risk of susceptibility in the population is represented by the proportion (or %) of the susceptible population. The incidence is equal to 0 if the susceptibility and/or transmission risk are also equal to 0. In reality, they are almost never equal to 0, and their actual relationship is never known.

The number of deceased persons depends on the proportion of people (CFR, %) who will inevitably die if they fall ill. This is a true CFR. Probably, the true CFR is a biological constant, which causes the lowest possible MR, if there is incidence. The actual CFR may, however, vary significantly and differ from the true CFR. The actual CFR depends on the ratio of the registered deceased persons and those with clinically identified disease. In most cases, mortality is recorded more effectively than disease incidence, so the stated CFR will always be higher than the actual CFR.

To calculate the vaccination contribution to the reduction in mortality, we used the parameters of reduction rate in incidence and mortality. Our algorithm for calculating the vaccination contribution to the reduction in mortality for each infection is based on the assumption of the direct epidemiological and proportional relationship between the reduction rate in these indicators over time. If the vaccine is successful, then its use will reduce the proportion (or %) of the susceptible population. All other things being equal, the incidence and mortality will decrease proportionally to the reduction in the proportion of the susceptible population. In real terms, the recorded mortality reduction rate may not be equal to incidence of reduction rate in proportion to the susceptible population. It is important to emphasize that the susceptible population proportion is not the only necessary risk factor for the onset of an infectious disease outbreak. The second critical risk factor is the probability of infection with an infectious agent. Under natural conditions, disease occurrence is possible only when both factors are present. In this case, the probability or risk of the disease is equal to the product of the risk of susceptibility and the risk of infection. Thus, the percentage of vaccine contribution to the reduction in proportion of the susceptible population, incidence, and mortality can range from 0% to 100%. Although this may not be accurately known, it can be estimated.

If the incidence of reduction rate is divided by mortality reduction rate and multiplied by 100%, then one can estimate the maximum possible approximate percentage

Table 1. Some Data on the State of Vaccination Among the Population of Ukraine (1936–2015)

	TB	*Diphtheria*	*Tetanus*	*Pertussis*	*Polio*	*Hepatitis B*	*Measles*
Years of introduction of routine vaccination	1960 (BCG liquid) 1962 (BCG dry)	1936 (D) 1963 (DTP, DT)	1952 (T) 1963 (DTP, DT)	1960 (P) 1963 (DTP)	1957–59 (IPV) 1960 (OPV)	2000 (HepB)	1969 (MCV1) 1986 (MCV2)
Immunization data (before 1965)	ND	1948–1964: 70.883.824 doses	1952–1964: 24.980.038 vaccinated	1961–1962: 2.537.912 doses	1957–1959: 104.000 children; 1960–1964: 54.634.972 children	NC	NC
Immunization data (1965–1991), % coverage (min/max/mean)	ND 91/99/95[a]	1965: 4.571.641 doses 42/99/63[b]	1965–1972: 69.346.107 doses 42/99/63[b]	1965–1972: 69.346.107 doses 42/99/63[b]	1965–1972: 18.904.893 children 81/86/84[a]	NC NC	1969–1972: 7.171.259 children 89/89/89[c]
Immunization data (1992–2005), % coverage (min/max/mean)	89/100/96	88/99/97	88/99/97	88/99/97	89/99/97	4/98/55[d]	90/99/90
Immunization data (2006–2015), % coverage (min/max/mean)	39/97/83	23/98/66	23/98/66	23/98/66	57/99/79	21/96/59	42/98/80

[a]1990–2015.
[b]1981–2015.
[c]1990.
[d]2000–2005.
TB, tuberculosis; ND, no data; NC, immunization not conducted.

contribution of vaccination and/or the susceptible population proportion to the reduction in mortality from infections. This is the case if the decrease in incidence was less than the decrease in the MR. If the incidence of reduction rate is higher than the mortality of reduction rate, then it is logical to assume that the vaccination contribution to the mortality of reduction rate may be 100% and/or not all cases of death were recorded. If on the other hand, the incidence of reduction rate was less than the mortality of reduction rate and/or there was a decrease in CFR, it is logical to assume that apart from vaccination, there were also effects of other factors that were not related to the vaccine action.

Thus, the maximum possible contribution of vaccination to the reduction in mortality is equal to the product of the rate of change in CFR and the quotient from the rate of reduction in CI divided by the rate of reduction in MR, then multiplied by 100%, in cases where the rate of reduction rate in CI was less than the MR of reduction rate. If the reduction rate of CI is greater than the MR reduction rate, then the maximum possible contribution of vaccination to the reduction in mortality is approximately equal to the product of the CFR reduction rate by 100%. Neither way of calculating the vaccination contribution to the reduction of mortality takes into account the effect of changes in the risk of the agent transmission. Thus, the actual and/or true contribution of vaccination may be substantially less than that being calculated.

In this study, calculations of the averages utilized the Microsoft Office Excel 2003 computer program. We used the methods of statistical analysis without calculating the confidence intervals for average values, but with definition of minimum and maximum values of indicators. We believe that this is sufficient to achieve the objectives of our estimative study.

Results

The data on immunization coverage in Ukraine are presented in Table 1. Some coverage with vaccinations against diphtheria and the incidence reduction were achieved in Ukraine even before the Second World War. During the Nazi occupation (1941–1944) no vaccinations were administered. In 1944–1950, the coverage of vaccination against tuberculosis, diphtheria, and tetanus increased, but was relatively low. In this regard, the incidence of diphtheria in 1944 was 150.0 per 100,000 people, that is, more than in 1939 (26.0 per 100,000 people) (9). Figures 1 and 2 show that the case numbers of deaths caused by diphtheria, tetanus, pertussis, and measles were the highest during the 1944–1964 period. For infections against which routine vaccination has never been performed (Fig. 3–pneumonia, influenza, and other acute upper respiratory infections), the number of deaths was highest in 1965–1991. As shown in Table 1, high total numbers of vaccine doses were administered against diphtheria in 1965 and against tetanus, pertussis, and poliomyelitis between1965–1972. Thus, according to the data shown in Table 1, a high coverage of vaccination against diphtheria, tetanus, pertussis, and poliomyelitis was only accomplished in the 1960s. The high coverage of immunization was maintained until the 1980s. Vaccination against diphtheria, tetanus, and pertussis fell slightly in the late 1980s and significantly increased from 1990 but then declined significantly from 2010. Vaccination against measles, polio, and tuberculosis also declined since 2010, with no vaccine purchases during this period.

The data in Table 2 show the difference in the numbers of deaths for both vaccine preventable and nonpreventable infections in 1965, 1991, and 2015. Data are for the overall population and subdivided into children aged 0–14 years

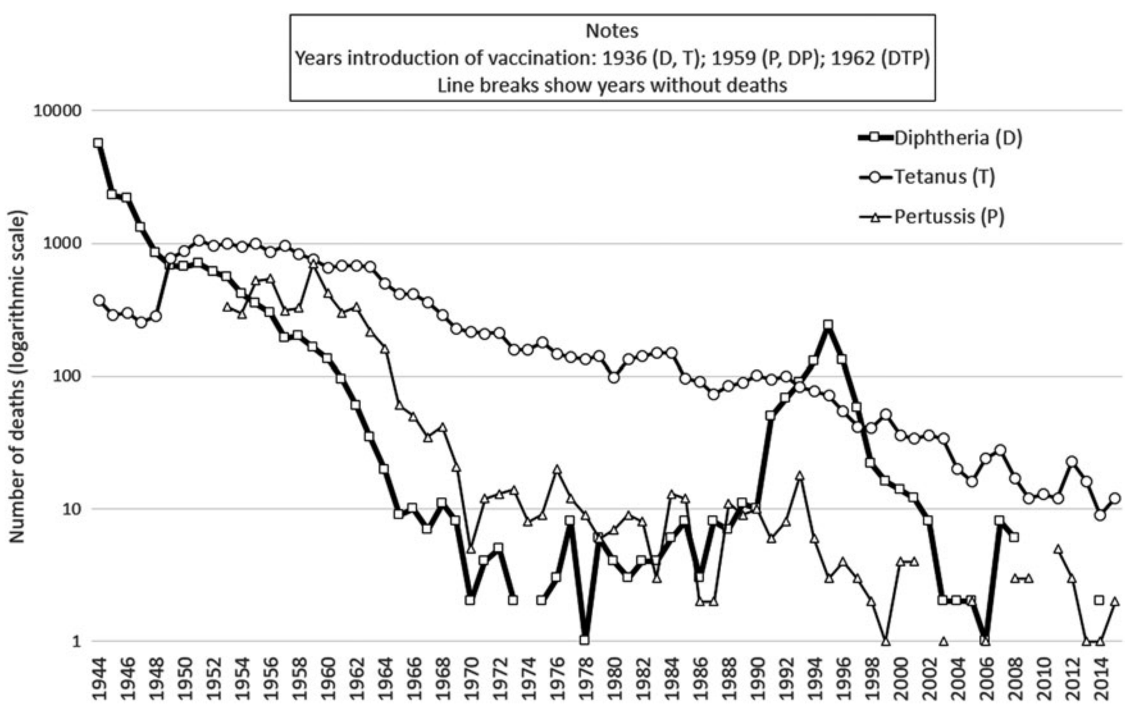

FIG. 1. Number of deaths from diphtheria, tetanus, and pertussis, in the years 1944–2015 and the years of the introduction of vaccination against each disease in Ukraine.

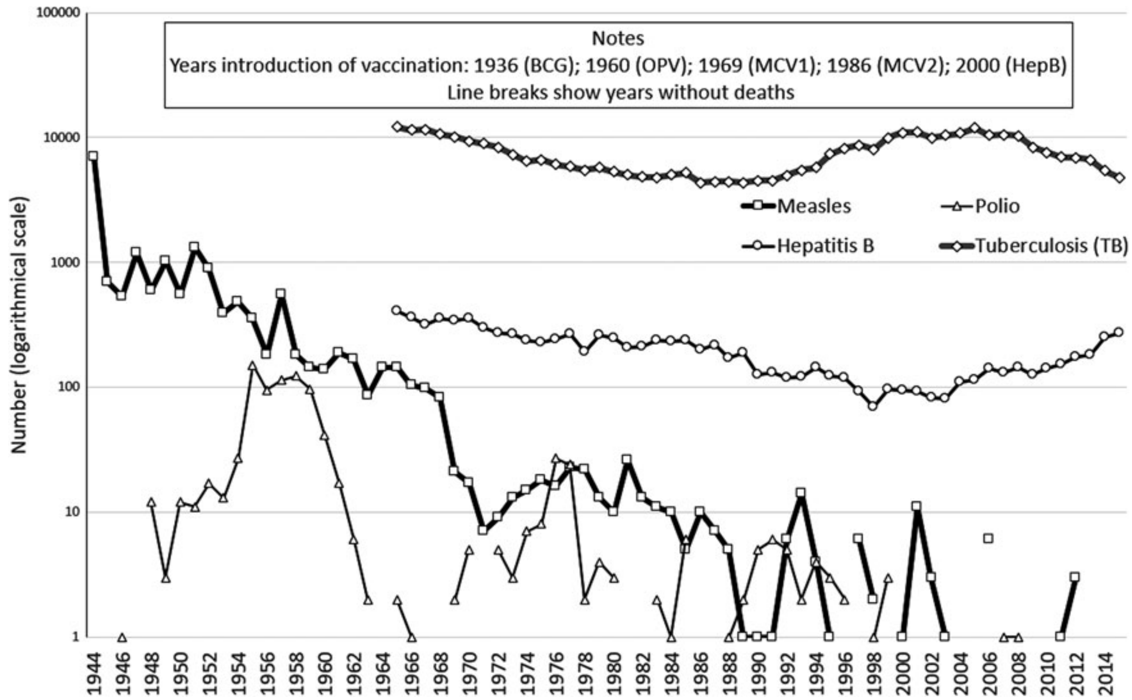

FIG. 2. Number of deaths from measles, polio, tuberculosis, and hepatitis B, in the years 1944–2015 and the years of the introduction of vaccination against each disease in Ukraine.

and people aged 15 years and older. Data on nosological forms of infections are also included in the table. As the cause of death, the relative contribution of infectious diseases decreased from 7.47% in 1965 to 1.53% in 1991, but increased to 2.51% in 2015. Infectious disease related mortality was significantly higher in the 0–14 age group, although this did decline by 5.4 fold to being 39.4% in 1965 and 7.25% in 2015. The proportion of VPI in the general structure of the cumulative population mortality decreased from 3.77% in 1965 to 0.85% in 2015, that is, by 4.4 fold. In children (0–14 years), the reduction in proportion of deaths from VPI declined from 2.12% in 1965 to 0.35% in 2015, that is, decreased by 6.1 fold. In 1965, 9,500 children aged 0 to14 years had died from non-VPI and 531 children of

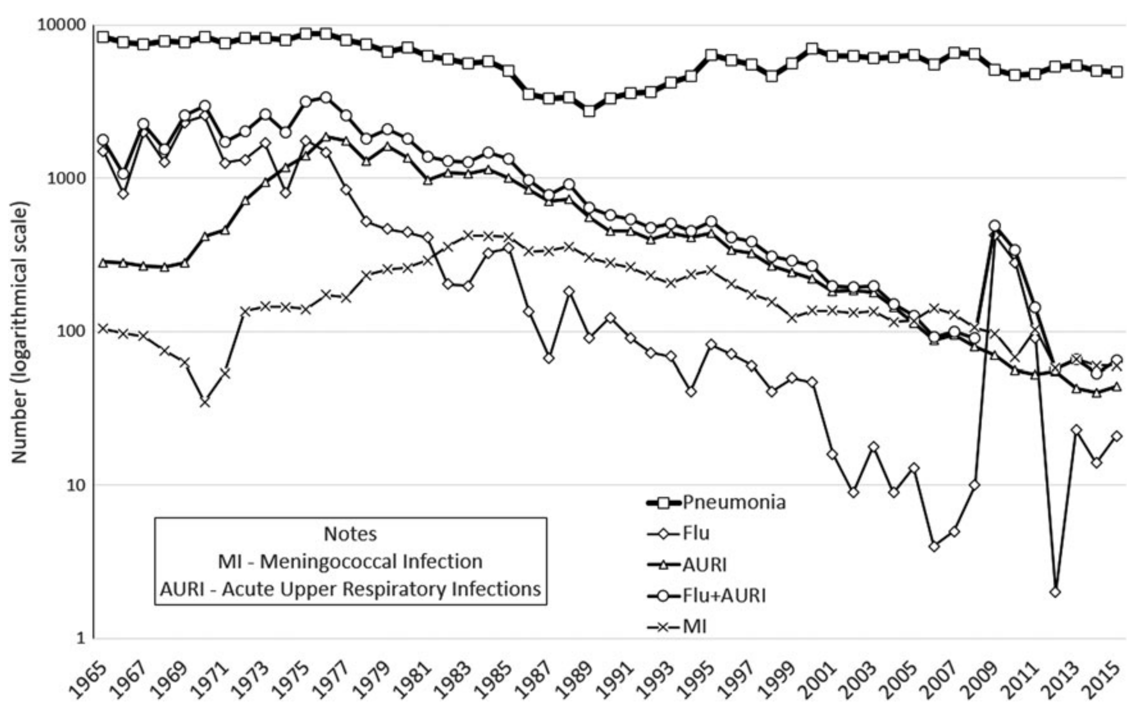

FIG. 3. Number of deaths from pneumonia, flu, and other acute upper respiratory infections and meningococcal infection in Ukraine (1965–2015).

TABLE 2. NUMBER OF VACCINE-PREVENTABLE AND NONVACCINE-PREVENTABLE INFECTIONS IN THE CONTEXT OF TOTAL AND INFECTIOUS MORTALITY IN UKRAINE IN 1965, 1991, AND 2015

		Number			Percentage of infectious mortality			Percentage of total mortality		
Nosological form	*Years*	*All ages*	*0–14*	*15 & ↑*	*All ages*	*0–14*	*15 & ↑*	*All ages*	*0–14*	*15 & ↑*
The number of deaths from all causes	1965	344,743	24,998	319,745				100	100	100
	1991	671,919	17,305	654,614				100	100	100
	2015	594,796	4,853	589,943				100	100	100
	1965/2015	0.6	5.2	0.5				1.0	1.0	1.0
Including all infectious and parasitic diseases* and pneumonia, flu, and Acute Upper Respiratory Infections	1965	25,745	9,858	15,887	100	100	100	7.47	39.4	4.97
	1991	10,256	2,065	8,191	100	100	100	1.53	11.9	1.25
	2015	14,919	354	14,565	100	100	100	2.51	7.29	2.47
	1965/2015	1.7	27.8	1.1	1.0	1.0	1.0	3.0	5.4	2.0
All nonvaccine-preventable infections	1965	24,966	9,500	15,466	96.97	96.37	97.35	7.24	38.0	4.84
	1991	9,998	2,013	7,985	97.48	97.48	97.49	1.49	11.6	1.22
	2015	14,641	351	14,290	98.14	99.15	98.11	2.46	7.23	2.42
	1965/2015	1.7	27.1	1.1	1.0	1.0	1.0	2.9	5.3	2.0
Vaccine-preventable infections (tuberculosis, diphtheria, tetanus, pertussis, poliomyelitis, and hepatitis B)	1965	12,985	531	12,454	50.44	5.39	78.39	3.77	2.12	3.89
	1991	4,782	68	4,714	46.63	3.29	57.55	0.71	0.39	0.72
	2015	5,082	17	5,065	34.06	4.80	34.78	0.85	0.35	0.86
	1965/2015	2.6	31.2	2.5	1.5	1.1	2.3	4.4	6.1	4.5
Vaccine-preventable infections without tuberculosis (diphtheria, tetanus, pertussis, poliomyelitis, and hepatitis B)	1965	779	358	421	3.03	3.63	2.65	0.23	1.43	0.13
	1991	258	52	206	2.52	2.52	2.51	0.04	0.30	0.03
	2015	278	3	275	1.86	0.85	1.89	0.05	0.06	0.05
	1965/2015	2.8	119.3	1.5	1.6	4.3	1.4	4.8	23.2	2.8
Potentially vaccine-preventable infections (pneumonia, influenza, Acute Upper Respiratory Infections, and meningococcal infection)	1965	10,266	7,938	2,328	39.88	80.52	14.65	2.98	31.8	0.73
	1991	4,367	1,485	2,882	42.58	71.91	35.18	0.65	8.58	0.44
	2015	5,079	213	4,866	34.04	60.17	33.41	0.85	4.39	0.82
	1965/2015	2.0	37.3	0.5	1.2	1.3	0.4	3.5	7.2	0.9

*All cases of death from infectious diseases that belong to the first class (some infectious and parasitic diseases - A00–B99) of the International Classification of Diseases of the 10th revision (ICH-10), as well as pneumonia, influenza (J09–J18), and acute respiratory infections of the upper respiratory pathways (J00–J06), which belong to the X class (respiratory diseases) (17).

the same age group had died from VPI, of which 173 deaths were attributed to tuberculosis. In 2015, 351 children had died from non-VPI and 17 children from VPI, of which 14 deaths were due to tuberculosis.

The data in Table 3 show a decline by 2.4 times of the death rate per 100,000 of all VPI among the total population, but for the pediatric population, the fold reduction was significantly higher in 2015 compared to 1965 and amounted to 17.2-fold. If deaths from tuberculosis are discounted, then the mortality from VPI in children was a 65.2-fold reduction. The overall death rate from all non-VPI decreased by 1.6 fold and fell by 14.8 fold among the pediatric population. Thus, the fold reduction in rates of the total infectious mortality, mortality from VPI, and mortality from non-VPI was approximately equal for the cumulative population, but was significantly higher for the pediatric population.

Data for 1965–1991 and 2006–2015

Comparative analysis of the annual averages of mortality for specific VPI was performed between earliest and most recent periods (1965–1991 and 2006–2015, respectively). As shown in Tables 4 and 5, some reduction in mortality of the pediatric population was observed; the highest for tetanus (reduced to 0) then hepatitis B (reduced by 18.2 fold) and measles (reduced by 14.1 fold). The non-VPI diseases (Tables 5 and 6) revealed a 60.1-fold decrease in children's mortality from influenza and a 15.4-fold decrease for pneumonia over the same time period. While comparing the 1965–1991 and 2006–2015 periods, tuberculosis (TB) did not show a decrease in mortality of the cumulative population, but there was a three-fold decrease in mortality from tuberculosis among children. This was significantly less than for any non-VPI, except meningococcal disease (Table 7). Total population data collected for these two time periods revealed mortality decreases associated with measles (22.7 fold), pertussis (3.9 fold), and diphtheria (1.4 fold). Slight increases in deaths due to tetanus and hepatitis B were observed.

A comparative analysis of the annual averages of mortality and incidence for VPIs between two periods (1944–1964 and 2006–2015 see Table 5) showed a significant

Table 3. Mortality Rate for Vaccine-Preventable and Nonvaccine-Preventable Infections in Ukraine in 1965, 1991, and 2015

Nosological form	*Years*	*Number*			*Mortality rate per 100,000*		
		All ages	*0–14*	*15 & ↑*	*All ages*	*0–14*	*15 & ↑*
The number of deaths from all causes	1965	344,743	24,998	319,745	764.41	210.28	962.76
	1991	671,919	17,305	654,614	1,301.57	156.90	1612.59
	2015	594,796	4,853	589,943	1,396.53	74.73	1634.35
	1965/2015	0.6	5.2	0.5	0.5	2.8	0.6
Including all infectious and parasitic diseases and pneumonia, flu, and Acute Upper Respiratory Infections	1965	25,745	9,858	15,887	57.09	82.92	47.84
	1991	10,256	2,065	8,191	19.87	18.72	20.18
	2015	14,919	354	14,565	35.03	5.45	40.35
	1965/2015	1.7	27.8	1.1	1.6	15.2	1.2
All nonvaccine-preventable infections	1965	24,966	9,500	15,466	55.36	79.91	46.57
	1991	9,998	2,013	7,985	19.37	18.25	19.67
	2015	14,641	351	14,290	34.38	5.40	39.59
	1965/2015	1.7	27.1	1.1	1.6	14.8	1.2
Vaccine-preventable infections (tuberculosis, diphtheria, tetanus, pertussis, poliomyelitis, and hepatitis B)	1965	12,985	531	12,454	28.79	4.47	3.74
	1991	4,782	68	4,714	9.26	0.62	11.61
	2015	5,082	17	5,065	11.93	0.26	14.03
	1965/2015	2.6	31.2	2.5	2.4	17.2	0.3
Vaccine-preventable infections without tuberculosis (diphtheria, tetanus, pertussis, poliomyelitis, and hepatitis B)	1965	779	358	421	1.73	3.01	0.13
	1991	258	52	206	0.50	0.47	0.51
	2015	278	3	275	0.65	0.05	0.76
	1965/2015	2.8	119.3	1.5	2.6	65.2	0.2
Potentially vaccine-preventable infections (pneumonia, influenza, Acute Upper Respiratory Infections, and meningococcal infection)	1965	10,266	7,938	2,328	22.76	66.77	7.01
	1991	4,367	1,485	2,882	8.46	13.46	7.10
	2015	5,079	213	4,866	11.93	3.28	13.48
	1965/2015	2.0	37.3	0.5	1.9	20.4	0.5
Population of Ukraine	1965	45,099,368	11,888,148	33,211,220			
	1991	51,623,547	11,029,533	40,594,014			
	2015	42,590,879	64,942,93	36,096,586			

reduction in mortality for the cumulative population. The reduction was greatest for measles (1,061.1 fold) and smallest for tuberculosis (0.8 fold). The differences in terms of the fold reduction in incidence of the cumulative population varied considerably from 1,295 times for polio to 0.8 times for tuberculosis. With respect to measles, pertussis, and diphtheria, the fold reductions in mortality were higher than the fold reduction in incidence. According to the data in Table 5, the average mortality from pertussis declined by 216 fold in 2006–2015 compared to 1944–1964, but the incidence decreased only by 47 fold, and fatalities due to pertussis decreased by 3.9 fold. If the fold reduction in incidence is divided by the fold reduction in mortality and then multiplied by the fold reduction in lethality, when multiplied by 100%, (i.e., $47/216 \times 3.9 \times 100\%$), then the maximum possible contribution of vaccination to the reduction in mortality from pertussis is determined to be 84.9%. This assumes that the risk of infection was constant during the 1944–2015 period. Table 5 presents the data on the vaccination contribution to the reduction in mortality from other VPIs. In general, it ranged from 0% (TB) to 84.9% (tetanus) for the total population. The vaccination contribution to the reduction in mortality for different age groups may differ significantly from the contribution for the cumulative population. For example, the death rate caused by tuberculosis among children aged 0 to 14 dropped significantly (from 173 deaths in 1965 to 14 deaths in 2015).

Discussion

Vaccination is widely regarded as an important approach to reduce the impact of many diseases. Using data collected over a more than 50-year period in Ukraine, this study aimed to investigate a correlation between vaccination and the diseases that they target. These data were not collected specifically for this purpose; consequently, there are some inherent difficulties associated with such studies. For example, technically it may be difficult to determine likely susceptibility to infectious agent without prior knowledge of the immune status of the individuals being tested. There are also compelling ethical restrictions on high-quality, placebo-controlled experiments using vaccinated the epidemiological efficacy of vaccines.

Table 4. The Cumulative Incidence, Case Fatality Rate, and Mortality Rate for Vaccine-Preventable Infections in Ukraine During the Periods (1944–1964, 1965–1991, 1992–2005, 2006–2015)

Indicators	*Periods*	*TB*	*Diphtheria*	*Tetanus*	*Pertussis*	*Polio*	*Hepatitis B*	*Measles*
Mortality Rate (minimum/maximum/mean) per 100,000 in all ages	1944–1964	ND	0.044/17/2.41	0.29/1.5/0.63	0.49/1.36/0.902	0/0.381/0.097	ND	0.19/21.5/2.29
	1965–1991	8.51/26.8/14.03	0/0.097/0.0147	0.10/0.37/0.177	0.004/0.14/0.032	0/0.055/0.0113	0.244/0.9/0.52	0.002/0.3/0.056
	1992–2005	9.58/25.3/17.88	0.004/0.5/0.111	0.02/0.12/0.06	0/0.035/0.008	0/0.0097/0.0056	0.14/0.24/0.21	0/0.027/0.007
	2006–2015	11.3/22.6/17	0/0.017/0.0037	0.01/0.04/0.016	0/0.011/0.0042	0/0.0022/0.0022	0.27/0.64/0.38	0/0.013/0.0022
Cumulative Incidence (minimum/maximum/mean) per 100,000 in all ages	1944–1964	ND	0.66/180/27.79	0.7/2.73/1.76	25/441/183.9	0.023/8.9/2.72	ND	154/1452/579.4
	1965–1991	31.94/45/38.71	0.016/3/0.197	0.18/0.92/0.36	4.42/67.9/19.59	0/0. 0159/0.0055	12.6/29.7/22.4	8.5/687.6/157.7
	1992–2005	31.9/84.1/58.24	0.21/10.3/2.76	0.034/0.2/0.099	0.84/13.4/4.34	0/0.0271/0.0086	9.6/25/19.27	0.31/45.1/13.9
	2006–2015	56.1/83.2/69.7	0.05/0.17/0.06	0.02/0.6/0.037	1.51/6.42/3.92	0/0.0021/0.0021	2.9/7.8/4.99	0.1/90.71/13.66
Case Fatality Rate (minimum/maximum/mean), % in all ages	1944–1964	ND	3.5/13.9/8.5	26.8/53/35.1	0.23/0.7/0.42	2/4.7/3.55	ND	0.036/1.8/0.36
	1965–1991	18.9/27.1/22.33	0/37.5/7.42	37.2/67.4/49.3	0.075/0.24/0.163	ND	0.82/4.41/1.91	0.014/0.2/0.036
	1992–2005	27.3/36.9/30.7	1.27/4.57/4.03	50/70.6/61.7	0/0.259/0.183	ND	0.75/2.54/1.08	0/0.122/0.05
	2006–2015	20.1/28.8/24.5	0/50/6.23	18.8/79.2/43.4	0/0.293/0.106	ND	3.9/20.18/7.52	0/0.075/0.016
Mortality Rate (minimum/maximum/mean) per 100,000, ages 0–14	1965–1991	0.15/1.49/0.43	0/0.067/0.032	0/0.37/0.058	0.018/0.5/0.13	0/0.163/0.036	0.25/0.82/0.61	0.009/1.2/0.216
	1992–2005	0.05/0.24/0.14	0/0.551/0.144	0/0.018/0.018	0/0.165/0.039	0/0.009/0.009	0.07/0.23/0.13	0/0.11/0.028
	2006–2015	0.08/0.22/0.14	0/0.061/0.0136	0/0/0	0/0.077/0.029	0/0.0154/0.0154	0.02/0.06/0.034	0/0.015/0.0153
Mortality Rate (minimum/maximum/mean) per 100,000, ages 15 yrs and older	1965–1991	11.1/35.9/18.2	0/0.096/0.0093	0.1/0.41/0.21	ND	0/0.024/0.008	0.24/0.94/0.496	0/0.017/0.006
	1992–2005	12.1/29.6/21.78	0.002/0.45/0.103	0.03/0.15/0.08	ND	0/0.01/0.0067	0.18/0.29/0.23	0/0.007/0.002
	2006–2015	13.27/26/19.85	0/0.01/0.002	0.01/0.5/0.02	ND	0/0.003/0.003	0.31/0.75/0.44	0/0.015/0.0023

TABLE 5. THE RATIO OF INDICATORS OF CUMULATIVE INCIDENCE, CASE FATALITY RATE, AND MORTALITY RATE IN VACCINE-PREVENTABLE INFECTIONS IN UKRAINE DURING THE PERIODS (1944–1964, 1965–1991, 1992–2005, 2006–2015)

The ratio of indicators	*Ratio of periods*	*TB*	*Diphtheria*	*Tetanus*	*Pertussis*	*Polio*	*Hepatitis B*	*Measles*
The ratio of mean Mortality Rate between different periods (all ages)	(1944–1964)/(1965–1991)	ND	164.5	3.6	28.3[e]	8.5	ND	41.3
	(1944–1964)/(1992–2005)	0.8[a]	21.7	10.4	114.6[f]	17.3	2.5[h]	330.3
	(1944–1964)/(2006–2015)	0.8[b]	656.3	40.5	216[g]	44.9	1.4[i]	1061.1
The ratio of mean Cumulative Incidence between different periods (all ages)	(1944–1964)/(1965–1991)	ND	141.3	4.9	9.4	495.1	ND	3.7
	(1944–1964)/(1992–2005)	1.0[c]	10.1	17.8	42.4	318.1	1.2[j]	41.7
	(1944–1964)/(2006–2015)	0.8[d]	471.1	47.7	47	1295.1	4.5[k]	42.4
The ratio of mean Case Fatality Rate between different periods (all ages)	(1944–1964)/(1965–1991)	ND	1.1	0.7	2.6[e]	ND	ND	9.9
	(1944–1964)/(1992–2005)	0.7[c]	2.1	0.6	2.3[f]	ND	1.8[j]	7.2
	(1944–1964)/(2006–2015)	0.9[d]	1.4	0.8	3.9[g]	ND	0.3[k]	22.7
The ratio of mean Mortality Rate between different periods (ages 0–14)	(1965–1991)/(1992–2005)	3.1	0.2	3.2	3.3	4.0	4.7	7.8
	(1965–1991)/(2006–2015)	3.0	2.3	up to 0	4.5	2.3	18.2	14.1
The ratio of mean Mortality Rate between different periods (ages 15 yrs and older)	(1965–1991)/(1992–2005)	0.8	0.1	2.8	ND	1.2	2.2	2.9
	(1965–1991)/(2006–2015)	0.9	4.6	11.6	ND	2.7	1.1	2.5
The maximum estimated proportion of the contribution of the share of susceptible (and/or vaccine) among all causes of mortality,%		0	100.5	80	84.9	ND	30	90.8

[a](1965–1991)/(1992–2005).
[b](1965–1991)/(2006–2015).
[c](1986–1991)/(1992–2005).
[d](1986–1991)/(2006–2015).
[e](1953–1964)/(1965–1991).
[f](1953–1964)/(1992–2005).
[g](1953–1964)/(2006–2015).
[h](1965–1991)/(1992–2005).
[i](1965–1991)/(2006–2015).
[j](1973–1991)/(1992–2005).
[k](1973–1991)/(2006–2015).

Without controlled experiments using vaccinated and nonvaccinated cohorts, one potential problem with our algorithm to evaluate vaccination effectiveness in reducing mortality is that we do not know the true relationship between disease cases and deaths.

Although we compare the morbidity and mortality due to various diseases, we realize that they are not identical among themselves. Any VPI differs both from different non-VPI and from other VPI. The extent of these differences between diseases is not known. For the purposes of this study, we assume that there is a relatively small degree of difference between the natural properties of different infectious diseases. All epidemics of these diseases are exposed to the same factors of external and internal environments. The strengths of these factors or their contributions to morbidity and mortality for different infections can also differ from each other over the different time periods being compared. Thus, it is assumed that the difference in morbidity and mortality indicators between VPI and non-VPI can be explained by the presence or absence of vaccinations. This methodological approach has the advantage over the historical comparison of morbidity and mortality before and after the vaccination introduction. Formally, the presence of a temporary association between the vaccination introduction and reduction in morbidity and mortality (28) is insufficient evidence to demonstrate a conclusive vaccination effect, so it is also necessary to assess the dynamics of morbidity and mortality for non-VPI and to compare it with that for VPI. In a certain sense, the non-VPI disease group is the historical control group for VPIs.

We presented some data concerning the immunization coverage and the dynamics of infectious mortality in Ukraine in the second half of the 20th and in the early 21st century. Below was stated that vaccination coverage in Ukraine was characterized by marked fluctuations, especially over the last 20 years. These large fluctuations in vaccine coverage over a long period of time almost certainly reduce the likelihood of a favorable outcome for the overall estimated impact of vaccines on the contribution of vaccination to the reduction of infectious mortality in the Ukraine. Our assessment of vaccine impact on infectious mortality is not based on a comparison of the dynamics of vaccination coverage and infectious mortality, but rather on a comparison of the dynamics and structure of infectious

Table 6. The Cumulative Incidence, Case Fatality Rate, and Mortality Rate for Nonvaccine-Preventable Infections in Ukraine During the Period (1965–2015)

Indicators	*Periods*	*Meningococcal infection*	*Pneumonia*	*Flu & other AURI*	*Flu*	*AURI*
Mortality Rate (minimum/maximum/mean) per 100,000 in all ages	1965–1991	0.07/0.84/0.44	5.4/18.6/13.3	0.13/5.4/1.8	0.13/5.4/1.8	0.0006/0.004/0.00175
	1992–2005	0.25/0.51/0.336	7.0/14.3/11.4	0.03/0.16/0.09	0.02/0.16/0.09	0.0003/0.0009/0.0006
	2006–2015	0.13/0.30/0.19	10.3/14/11.8	0.01/0.9/0.22	0.01/0.92/0.19	0.0001/0.0002/0.00014
Cumulative Incidence (minimum/maximum/mean) per 100,000 in all ages	1944–1964	ND	ND	2,280/17,557/6,611	ND	ND
	1973–1991	2.98/5.7/4.57	ND	10,706/31,617/22,644	277/6592/3733	14,824/26,849/21,626
	1992–2005	1.9/3.13/2.43	ND	15,748/21,908/18,686	752/3354/1903	18,838/18,738/16,771
	2006–2015	0.77/1.86/1.19	ND	14,150/20,188/17,019	29.5/1014/300	14,120/19,564/16,718
Case Fatality Rate (minimum/maximum/mean), % in all ages	1973–1991	6.13/17.1/12.12	ND	0.004/0.03/0.02	0.005/0.07/0.03	0.0039/0.0195/0.104
	1992–2005	11.3/17.88/13.83	ND	0.002/0.005/0.004	0.002/0.01/0.005	0.0014/0.005/0.0033
	2006–2015	15.08/18.29/16.25	ND	0.001/0.005/0.002	0.001/0.15/0.06	0.0006/0.0012/0.0008
Mortality Rate (minimum/maximum/mean) per 100,000, ages 0–14	1965–1991	0.15/3.24/1.538	9.5/61.3/36.8	3.97/22.8/11.3	0.51/12.7/4.43	2.006/15.322/6.853
	1992–2005	1.27/1.93/1.39	2.4/9.4/6.6	1.1/3.9/2.5	0.05/0.38/0.2	1.03/3.38/2.288
	2006–2015	0.69/1.69/1.070	1.9/3.1/2.3	0.27/0.9/0.58	0/0.22/0.074	0.257/0.863/0.505
Mortality Rate (minimum/maximum/mean) per 100,000, ages 15 years and older	1965–1991	0.07/0.22/0.14	3.3/8.1/6.1	0.12/2.46/0.97	0.04/3.77/0.97	0.111/1.605/0.288
	1992–2005	0.07/0.13/0.09	6.5/15.3/12.3	0.012/0.12/0.06	0.012/0.12/0.06	0.102/0.176/0.139
	2006–2015	0.02/0.08/0.05	11.6/15.9/13.4	0.005/0.7/0.23	0.005/1.04/0.2	0.047/0.095/0.075

AURI, acute upper respiratory infections.

TABLE 7. THE RATIO OF INDICATORS OF CUMULATIVE INCIDENCE, CASE FATALITY RATE, AND MORTALITY RATE FOR NONVACCINE-PREVENTABLE INFECTIONS IN UKRAINE DURING PERIODS (1944–1964, 1965–1991, 1992–2005, 2006–2015)

The ratio of indicators	*Ratio of periods*	*Meningococcal infection*	*Pneumonia*	*Flu & other AURI*	*Flu*	*Other AURI*
The ratio of mean Mortality Rate between different periods (all ages)	(1965–1991)/(1992–2005)	1.3	1.2	21.2	21.2	3.2
	(1965–1964)/(2006–2015)	2.3	1.1	8.2	9.4	12.9
The ratio of mean Cumulative Incidence between different periods (all ages)	(1944–1964)/(1965–1991)	ND	ND	0.4	ND	ND
	(1973–1991)/(1992–2005)	1.9	ND	1.2	2.0	1.3
	(1973–1991)/(2006–2015)	3.9	ND	1.3	12.5	1.3
The ratio of mean Case Fatality Rate between different periods (all ages)	(1973–1991)/(1992–2005)	0.9	ND	4.5[a]	6.4	3.2
	(1973–1991)/(2006–2015)	0.7	ND	8.5[b]	0.5	12.8
The ratio of mean Mortality Rate between different periods (ages 0–14)	(1965–1991)/(1992–2005)	1.1	5.6	4.5	22.3	3.0
	(1965–1991)/(2006–2015)	1.4	15.7	19.5	60.1	13.6
The ratio of mean Mortality Rate between different periods (ages 15 years and older)	(1965–1991)/(1992–2005)	1.5	0.5	17.1	17.1	2.1
	(1965–1991)/(2006–2015)	2.9	0.5	4.2	4.6	3.9

Underline shows the ratio of indicators between periods of time.
[a](1965–1991)/(1992–2005).
[b](1965–1991)/(1992–2005).

mortality and incidence. We assume a priori that vaccination reduces the infectious mortality by reducing the incidence. Thus, we estimate the impact of vaccination on epidemiological indicators indirectly, that is, taking into account the rate of change or the fold change of the disease risk and the death risk after the introduction of routine vaccination. The greater the reduction in the risk of getting sick, the more likely the impact of vaccines will impact on reducing mortality, because the indicators of incidence, mortality, and lethality are interconnected as epidemiological, logical, and mathematical magnitudes. If vaccination is effective, then the mortality will decrease proportionally to the incidence reduction. In turn, the incidence is reduced due to the fact that vaccination reduces the number of susceptible people in the population for some infections (such as measles and polio) and, simultaneously, also helps to prevent the spread of the pathogen.

If the fold reduction in mortality for some infections exceeds the fold reduction in incidence, we can call this reduction in mortality as ''excessive'' as it is not related to the fold reduction in incidence. If we proceed from our hypothesis of the direct proportional relationship between incidence and mortality, the presence of ''excessive'' mortality is probably indicative of the contribution to the reduction in mortality of those factors that do not depend on the vaccination coverage and/or this indicates the significant underestimation of incidence. It may mean that after the introduction of mass vaccination its contribution to the reduction in mortality from certain VPI may be less than the estimated 100% value.

The case-fatality rate for measles decreased by 95% in 1969 compared to 1944. Obviously, this is due to the radical improvement of material conditions of children's life, advancement of hospital conditions, and superior treatment methods, for example, such as antibiotic treatment of pneumonia and seroprophylaxis (4). This conclusion is, in part, supported by the observation that a significant reduction in mortality and incidence was observed even before the introduction of vaccination.

We believe that the accuracy of our calculations for this type of analysis is quite acceptable for approximate estimation of the immunization contribution to the reduction in mortality, but given the presence of the very large variability of annual epidemiological indicators, the quality of our assessments derives from natural (epidemiological) and logical prerequisites, rather than from the actual reliability of the data used. In our opinion, the existence of almost direct proportion relationship found between the gradients of incidence, mortality, and lethality for diphtheria, tetanus, pertussis, and measles is not random, but probably indicates that the vaccination may be an important factor of influence on the epidemic process that reduces natural, cyclic, and occasional manifestations of epidemics. The more pronounced is this dependence, the more controlled is the infection. To test our hypothesis, it is also important to emphasize that the data on the number of illnesses and deaths were obtained from different and mutually independent sources. Registering the infectious incidence was carried out by the sanitary and epidemiological service agencies of the Ministry of Health of Ukraine, and the death registration was the function of the State Statistical Office.

Our hypothesis assumes that, all other things being equal, the proportion of fatal infections among those infected, or true lethality (CFR), for each infection and each country is a definite value that changes slowly over time (for years or decades). The assumption that the vaccination itself reduces mortality, probably, is contrary to our findings for some infections (diphtheria, tetanus, measles, and, possibly, pertussis) assuming that these data are robust. We suggest that if the incidence is not equal to 0, then reduced mortality is not solely the result of vaccination. In these circumstances, we believe that prophylactic vaccination cannot prevent death faster than the disease itself that can cause the death. It is biologically implausible. We believe that this can be explained by underreporting of the incidence and/or by influence of other causes that are unrelated to the vaccines. This is supported by the data for diphtheria, pertussis, measles, and tetanus infections. These data illustrate the relatively small mortality reduction postvaccination administration (by 1.4 fold for diphtheria, 2.25 fold for measles, and 3.9 fold for pertussis), or even its increase (tetanus, hepatitis B), which can be explained by a lack of influence of the vaccination, but rather through the completeness of these diseases' registration and the effectiveness of the treatment of cases. In our opinion, these deficiencies can be offset to some extent, due to the high power of represented data file and the large time length of certain periods, which were used to calculate the average indices of mortality, lethality (CFR), and incidence.

Conclusions

The vaccination contribution to the reduction in mortality from VPI is characterized by statistical and causal (epidemiological) accordance of indicators of incidence, mortality, and lethality. During the 1944–2015 period in Ukraine, the mortality reduction rate for VPI was very impressive. It could range from 40.5 fold (tetanus) to 1,061.1 fold (measles). However, the incidence reduction rate was significantly lower in general and ranged from 42.4 fold (measles) to 471.1 fold (diphtheria). This is probably due to external factors unrelated to vaccines, including improved medical facilities, treatments and health information collection, quality of life, environment, and so on. Importantly, the vaccination contribution to the reduction in infectious mortality was more significant for the pediatric population, among which the annual mortality from VPI is currently absent or very rare except for cases of tuberculosis.

In Ukraine, vaccination remains a strong factor of pressure on the epidemic process of some VPI. It helps to maintain the low level of infectious mortality over the past 30–50 years and prevents the resurgence of epidemics, but, unfortunately, not in the case of diphtheria (1990s), measles, and tuberculosis (1990–2000s). Thus, in Ukraine, vaccination against certain infections, of course, had and will continue to have an importance in the future for the control of infectious disease incidence and mortality. Moreover, vaccination remains the most accessible and effective intervention to achieve global or regional elimination of some infections (e.g., polio, measles, and tetanus). Given the existing historical and epidemiological data on mortality from vaccine-preventable infections and their proportion in the current structure of general and infectious mortality, we assume that in the next few decades, maybe, the impact of programs for vaccination on reducing the infectious mortality in Ukraine will be much smaller than over the past 70–100 years.

Acknowledgment

DTRA, Metabiota, Ministry of Health of Ukraine.

Author Disclosure Statement

No competing financial interests exist.

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