
Biosurveillance of Meningococcal Infection in Ukraine, 43 Years of Survey: Spatial and Temporal Dynamics Models

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Abstract

Meningococcal disease in Ukraine represents an important cause of mortality mostly among the child population of less than five-year old. The present study illustrates the advancement on understanding of Meningococcal epidemiology across the national level by using 20 years of data provided by the Ministry of Health of Ukraine on a constant survey of the disease. This unique set of data includes: demography (census); disease incidence from 1973 to 2015 (i.e., purulent meningitis etiologic diagnostic); Meningococcal disease mortality; anonymized demographic data (sex, age, leaving area/city/village); Comparative etiology of purulent meningitis; serogroups of invasive meningococcal disease; carriers prevalence; a set of clinical data (meningitis, meningococemia, nasopharyngitis, etc.); and a set of environmental data (season, etc.). The dynamic of the disease is described for over the past 20-year period of time including incidence, prevalence, spatial distribution, seasonality, and risk factors. Existing state of the art of meningococcal infection epidemiology is presented for the all country. Ultimately, time series analysis of record and spatial distribution over such a long period of time supported the development of original construct of various models encompassing risk and vulnerability, and ways to improve epidemiological surveillance, and develop vaccination strategies in country.

Keywords: meningitis, meningococemia, time series, modeling, Ukraine

1. Introduction

1.1. Background

To date, purulent bacterial meningitis (PBM) remains a global health challenge. Meningococcal meningitis occurs in small clusters throughout the World with seasonal variation, accounts for a variable proportion of epidemic bacterial meningitis, and is one of the leading causes of such meningitis globally with a burden that, in 2012 encompassed 395,230 deaths, or 0.7% of global mortality [1, 2].

Meningococcal disease or meningococcal meningitis is caused by bacterium *Neisseria meningitidis*, also called meningococcus. Meningococcal bacteria may cause infection, which occurs in different compartment of the body, called invasive meningococcal disease (IMD), including skin, gastrointestinal tract, or respiratory tract, among others. Ultimately, the bacteria may pass through the bloodstream and reach the nervous system causing meningococcal meningitis. After an incubation period of 2–10 days, clinical presentation starts with symptoms similar to influenza (flu-like), which cause nausea, vomiting, rash, increased sensitivity to light, and confusion. Symptoms of meningococcal disease appear usually as a sudden onset of fever, headache, and stiff neck. When treated, most patients with meningococcal meningitis recover completely with appropriate antibiotic therapy and rapid medical attention. Also, meningitis can cause severe brain damage and be fatal for 50% of untreated cases.

There is no animal reservoir, and *N. meningitidis* is obligate commensals of human and can colonize the nasopharyngeal mucosa without affecting the host, a phenomenon known as carriage. Such asymptomatic carriage of meningococcus is the most prevalent form of meningococcal infection. In none-epidemic settings, approximately 10–35% of healthy individuals carry *N. meningitidis* in the upper airway [3, 4]. Thus, only in very rare cases, *N. meningitidis* is the cause of invasive meningococcal disease. *N. meningitidis* is transmitted from person-to-person through respiratory droplets or throat secretions from carriers or eventually patients. The risk of transmission and spread increases in particular by close and prolonged contact (e.g., kissing, sneezing, coughing, promiscuity, and sharing food or drinking utensils) with an infected person (symptomatic or asymptomatic (i.e., carrier). Moreover, such risk increases with recent upper respiratory infection, while young children and teen-agers are at greatest risk of infection.

Several types of meningococcal vaccines are available including Meningococcal Polysaccharide vaccines as bivalent (groups A and C), trivalent (groups A, C and W), or tetravalent (groups A, C, Y and W). Tetravalent A, C, Y, and W conjugate vaccines have been licensed since 2005 for use in children and adults in Canada, the United States of America, and Europe. Since 1999, meningococcal conjugate vaccines against group C have been available and widely used. (e.g., Meningococcal conjugate vaccine; Meningococcal polysaccharide vaccine; Serogroup B Meningococcal B) and are recommended vaccines as the best that can prevent meningitis infection. As of June 2015, over 220 million persons aged 1–29-year old received meningococcal A conjugate vaccine against the most meningitis type prevalent among 15 countries of the African belt [2].

1.2. Epidemic pattern of Meningococcal meningitis in Europe

There is a reported reduction of morbidity of Invasive Meningococcal Disease (IMD) in the European countries (i.e., EU/EEA): The total number of confirmed cases of the IMD fell from 7995 to 3463 for the period from 1999 to 2012. In countries with a meningococcal serogroup C vaccination program, the number of cases fell from 4840 to 2380, in countries where systematic immunization campaigns are not applied incidence decreased from 3155 cases to 1083 cases [5, 6]. Therefore, a reduction of IMD mortality in EU/EEA countries was reported that diminished from 0.163 to 0.055 per 100,000 people from 1992 to 2012 [7]. Although, IMD is relatively rare in Europe (0.68 cases/100,000 people in 2012), country-specific rates of confirmed IMD range from 0.11 to 1.77 cases per 100,000 people [8].

Worldwide, most IMD cases are caused by serogroups B and C. Serogroup Y prevalence has been increasing but remains less frequent than B and C. An overall decreasing trend has been observed over the last 10 years, partly attributable to the introduction of serogroup C conjugate vaccine to national immunization schedules in several European countries.

Finally, it is of importance to strengthen surveillance of meningococcal disease in order to reduce burden of the disease (including patient and carrier) and to evaluate the impact of the ongoing vaccination programs, and support decision-makers with respect to the availability of new vaccines [6].

2. Meningococcal infection biosurveillance and Public Health response and control in Ukraine

The purpose of epidemiological surveillance of meningococcal infection (MI) is to prevent deaths and reduce disease morbidity risk groups. A retrospective epidemiological analysis of MI must include data monitoring morbidity risk groups (e.g., children aged of 0–1 and 1–4 years old), and other young people as which came as socio-organized as group indicators (i.e., including school, kindergartens, orphanages, vocational colleges, university, among others). Equally important is the analysis of total mortality and mortality by risk groups and their dynamics. In addition, data are analyzed from microbiological monitoring of “indicator groups.” Moreover, there is a national serological monitoring of MI pathogens.

In epidemic foci of MI, patients with IMD are hospitalized and isolated while and a 10 days’ medical observation of contact-persons is conducted (thermometry and examination of the skin and mucous membranes of the nasopharynx). Bacteriological tests are done twice among organized groups and once at home (i.e., family contact) within epidemic foci. Surveillance of other purulent meningitis is carried out as for meningococcal infection.

In Ukraine, since the 1920s, MI cases introduced are registered as well as *Haemophilus influenzae* type B Hib-meningitis cases are registered since 2010. From 2012, pneumococcal meningitis (PM) and all other bacterial meningitis are also registered. Vaccination against Hib-infection was included in the routine immunization program in 2006 by the Ministry of Health, while it is considering now to introduce a national vaccination campaigns against meningococcal and

pneumococcal disease. As of 2013, an estimated of 68.9% of Ukrainians lives in urban areas including the 68.2% of the population over 45 years old [8].

Since 2007, there is a Central Reference Laboratory for invasive bacterial diseases (IBD) characterizing and supervising the dynamic of IBD pathogens in order to forecast and reduce (preventive measures) the incidence of IBD. The State institution “Ukrainian Centre for Disease Control and monitoring of the Ministry of Health of Ukraine” is a reference as part of the IBD-laboratory WHO and UNICEF networks. A sentinel surveillance system included all patients younger than 5 years clinically suspected of meningitis and hospitalized as hospital in-patient of either the department of infectious disease or intensive care unit.

3. Temporal and spatial dynamics of meningococcal infection in Ukraine

3.1. Place and time of meningococcal infection and other purulent meningitis

Purulent bacterial meningitis (PBM) is a group of diseases of multi-bacterial etiology that determines the nature of the treatment, laboratory diagnostic approach and epidemiological characteristics for control and prevention. Indeed, PBM transmission and clinical presentation are fully dependent on the etiologic agent and concurrent risk factor. PBM etiology will ensure a successful causal treatment and important information regarding the whole nosology of the meningitis and epidemiology pattern. Bacteriological etiological diagnosis of PBM has been carried out for 24 years (1992–2015) in Ukraine (Ukrainian Centre for Disease Control and monitoring of the Ministry of Health): 37,843 cases were registered as PBM, among them, 18,878 were of purulent meningitis of meningococcal origin and other IMD. The ratio of meningococcal meningitis to non-meningococcal meningitis was about more or less of 1:1 (i.e., 49.89 to 50.11%) (Figure 1).

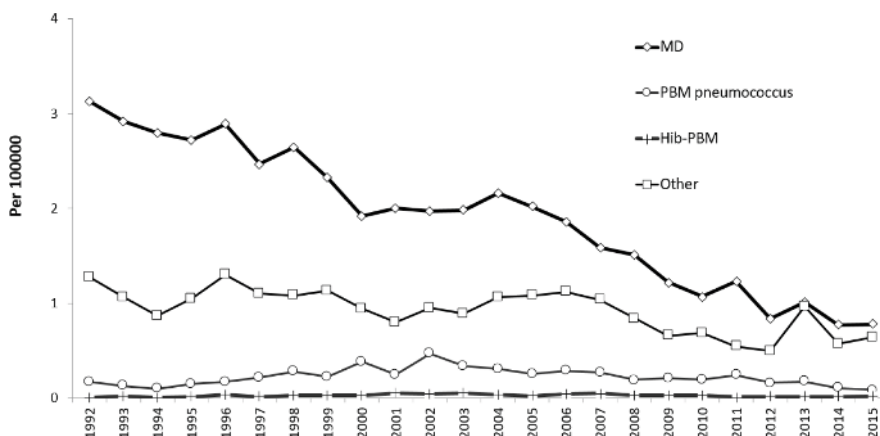


Figure 1. Incidence dynamics of different etiologies of bacterial meningitis (Ukraine, 1992–2015). Legend: Abscissa = time (year); Ordinate = case of bacterial meningitis per 100,000 people; Empty diamond = Meningococcal Disease (MD); Empty square = Other Meningitis (caused by *Staphylococcus aureus*, *Streptococcus* groups A and B, *Klebsiella pneumoniae*, *Escherichia coli*, *Listeria monocytogenes* and PBM of unknown etiology); Empty circle = PBM pneumococcus (Purulent Bacterial Meningitis caused by *Streptococcus pneumoniae*); Cross = Haemophilus influenzae type b (Hib).

The use of microbiological monitoring of PBM in Ukraine allowed to determine the etiological origin of 37,843 cases from 1992 to 2012. The basic etiological agents PBM included: Meningococci (49.89%); Pneumococci (6.34%); Staphylococci, Streptococci and others (*Escherichia* spp., *Listeria* spp., etc.) (17.30%); Hib-infection (0.71%), and pathogens of unknown etiology (25.77%). Among the 21,359 registered cases of MI, 9986 cases (46.75%) were confirmed to be of bacteriological origin. Bacteriological confirmation of MI ranges from 33.71% in 1993 to 55.95% 9 years after (2002) (**Figure 2**).

Meningococcal infection predominated among all bacterial meningitis during the whole period of observation. However, half of all non-meningococcal meningitis as well as IMD did not have bacteriological confirmation the bacteriological tests were done almost in all patients but were not positive for half of all meningococcal meningitis. Thus, the total sensitivity of bacteriological tests was inadequate (nearly 50%).

3.2. Time series of morbidity and mortality of meningococcal infection in Ukraine

In 1969, an incidence of less than 0.9 per 100,000 people of MI was recorded. Since then, the incidence began to rise and lasted until 1985. For decade (1973–2012), MI incidence (including all clinical forms) ranged from 6.7 (1985) to 0.83 (2012) per 100,000 people. Instead, in the long term, of IMD and mortality appear be very specific and different dynamics, while IMD incidence is much lower and ranges from 2.22 (1974) to 0.75 (2012) per 100,000 people with a mortality from 0.84 (1983) to 0.09 (**Figure 3**).

There is a significant decrease morbidity and mortality of MI for the last 33 years in Ukraine. Between 1983 and 2015 the incidence of MI decreased by 7.2 times. Between 1973 and 2015

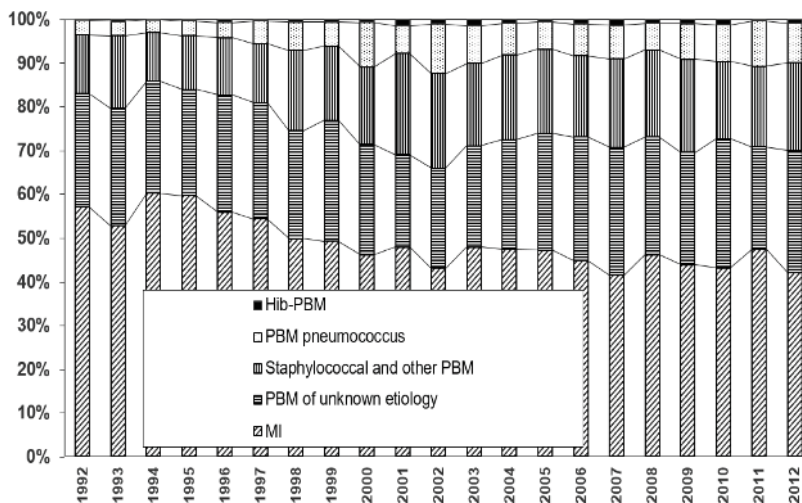


Figure 2. Etiological structure of purulent meningitis cases in Ukraine (1992–2012). Legend: Abscissa = Time (year); Ordinate = relative percentage of the bacterial meningitis etiology; oblique lines = Meningococcal Infection (MI); vertical lines = Staphylococcal and Other PBM (caused by *Staphylococcus aureus*, *Streptococcus* groups A and B, *Klebsiella pneumoniae*, *Escherichia coli*, *Listeria monocytogenes* and other PBM); horizontal lines = PBM of unknown etiology); points = PBM pneumococcus (Purulent Bacterial Meningitis caused by *Streptococcus pneumoniae*); black = *Haemophilus influenzae* type b (Hib-PBM).

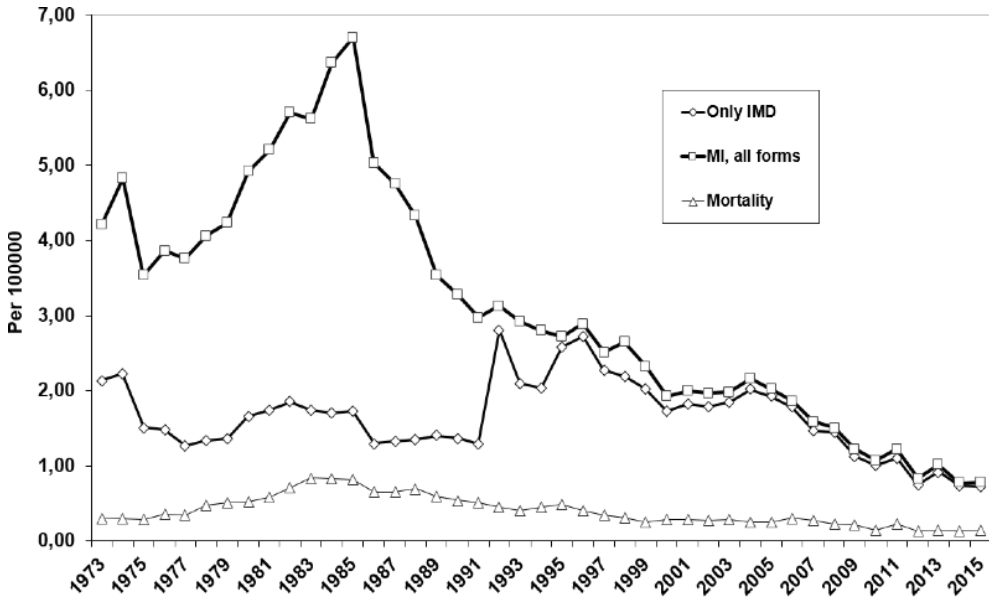


Figure 3. Morbidity and mortality dynamics of meningococcal infection in Ukraine of a decade of observation (1973–2015). Legend: Abscissa = time (year); Ordinate = patient meningococcal infection per 100,000 people; line with empty square = Meningococcal Infection (total MI, all clinic forms); line with empty diamond = Invasive Meningococcal Disease (IMD); line with empty triangle = total Mortality of Meningococcal Infection.

the incidence of MI decreased by 5.4 times. In 2012 in Ukraine, IMD incidence (0.75 per 100,000) was comparable to the one of EU (0.7 per 100,000). However, death rate in Ukraine (0.09 per 100,000) was higher than in the EU (0.06 per 100,000). Also, this has to take into account that half of the cases of MI in Ukraine are not bacteriologically confirmed.

3.3. Seasonality of meningococcal infection in Ukraine

From 1992 to 2015, most IMD cases occurred in winter and spring, as for other respiratory diseases in Ukraine. IMD incidence peaked up in March, while the lowest number of cases was reported in August (**Figure 4**). During that same period of time, 938 cases of IMD were regularly reported on the monthly base, and seasonal increase was registered when the number of monthly cases exceeded 78 (938 cases / 12 month = 78.2 ≈ 78). Seasonal incidence rise was lasted for 6 months (from December to June) with a cumulative total number of 554 cases corresponding 59.06% annual incidence (i.e., seasonal coefficient with regard to the 9.84% average for each of these months. A 334 (40.94%) as of MI cases occurred during the seasonal rise with a monthly increase of 6.82%. One can ultimately evaluate the cases associated with seasonal risk factors that were in 18.66%, i.e. (9.84% – 6.82%) × 6 months = 18.66%.

Thus, the impact of seasonal factors on the annual incidence is very moderate, that is, annual incidence of MI is due to the seasonality of not more than one-fifth of part. Over 80% of

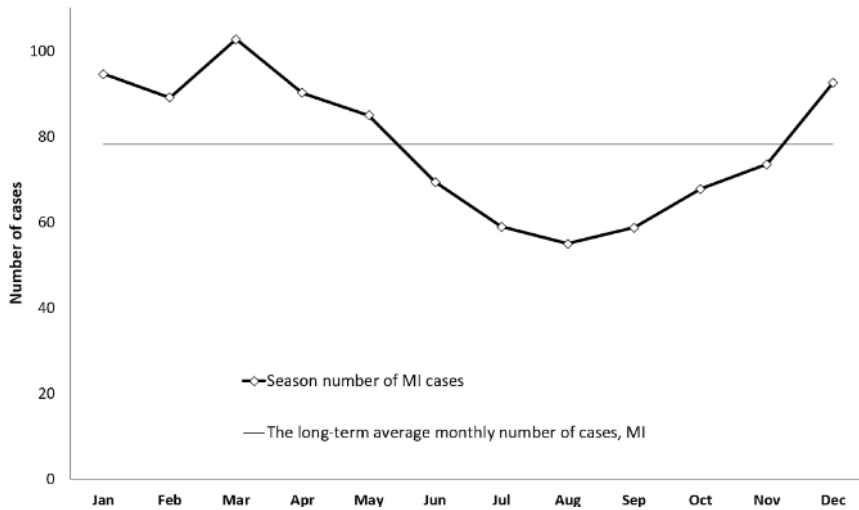


Figure 4. Seasonal distribution of meningococcal infection in Ukraine (1992–2015). Legend: Abscissa = time (months); Ordinate = absolute number of cases of meningococcal infection; Gray line = the average monthly number of Meningococcal Infection (MI) cases of long-term; Empty diamond = number of Meningococcal Infection (MI) cases by month.

incidence of MI depends on the action of permanent factors. Our hypothesis is that the proportion of susceptible population and the frequency of contacts between people (at risk of infection) are the basic are a permanent risk of MI transmission. We also assume that its values are slightly slowly changing throughout the year. Such seasonal rise was observed in Europe from December to June is also characterized by a seasonality pattern as it is in Ukraine, with the highest rate reporting during winter [8].

3.4. Geographical distribution

The incidence of MI is unevenly distributed on a geographical ground and expressed by ANOVA MI incidence for the 1992–2013 period of times among administrative units of Ukraine. Estimated value (Fisher's test = 8.52, > critical value of 1.52) rejects the null hypothesis of no effect of geographical factors on the incidence of MI. Indeed, **Figure 5** shows the uneven geographical distribution of the disease by administrative units with low, medium, and high levels of incidence.

At first, the geographical distribution of MI incidence depends on population age pyramid including, the total population of the study area, the urban population and the child population of 0–14 or 0–4-year old. We therefore calculated the corresponding correlation coefficients, but ultimately lacked of statistical significance between prevalence and administrative units. MI incidence correlation coefficients, when compared to different group, were equal to: 0.3260 versus population density; 0.036 versus total population; 0.1711 versus urban population percentage; 0.1370 versus children aged 0–14; and 0.1968 versus the children aged

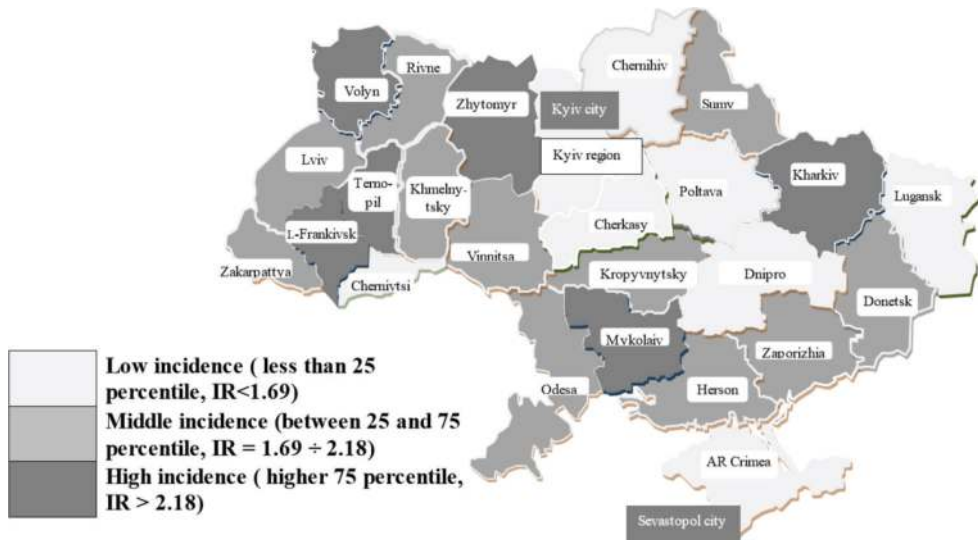


Figure 5. Incidence of meningococcal disease in Ukraine by oblast (1992–2013). Legend: light-gray = Low incidence of Meningococcal Disease (less than 25 percentiles, $IR < 1.69$); moderately gray = Middle incidence of Meningococcal Disease (between 25 and 75 percentile, $IR = 1.69 \div 2.18$); gray = High incidence of Meningococcal Disease (higher 75 percentile, $IR > 2.18$).

0–4 years. We believe that the lack of statistical significance between these indicators suggest sporadic (or random) spatial nature distribution of the disease. Also, ANOVA analysis shows significant differences in the incidence among oblasts, but the correlation analysis of individual factors (population density, age structure, etc.) by oblasts did not show any incidence because the population density and age structure are indirect factors. Thus, we can assume that geographical factors of each individual territory are quite stable, while geography has a limited effect on changes in incidence of MI in Ukraine. Geographical distribution of MI incidence is useful for comparing performance in different areas, but it cannot account for observed differences more likely linked to the multicomponent result with other causal factors. Also, the variable power of causal factors in any oblast could explain the differences in the incidence oblasts. In our case, the geographical distribution of the incidence of MI is a little informative because do not allowed to identify direct factors (i.e., risk of infection and/or risk of susceptibility).

3.5. Age distribution

The total incidence of MI decreased over the study period in Ukraine among all age groups, while it remains the highest among young children (**Figure 6**).

In Ukraine, the proportion of MI infected children under 14 years represented 77.17% of all cases as compared to 49.81% among the same xc of age of other European countries at

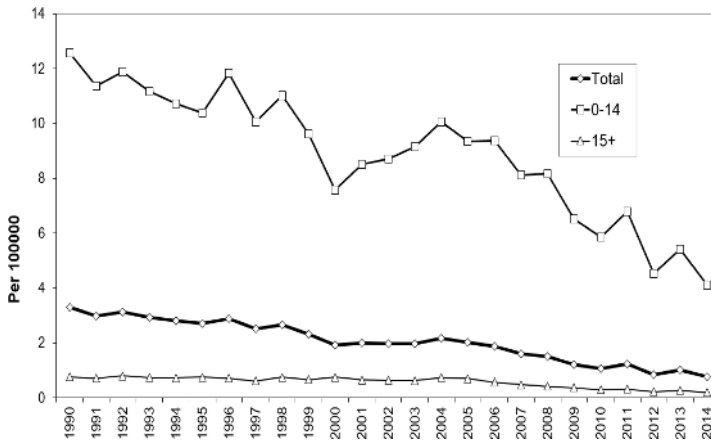


Figure 6. Dynamics of the incidence of meningococcal infection in Ukraine by age group (1990–2014). Legend: Abscissa = time (year); Ordinate = person with meningococcal infection per 100,000 people by age group; Triangle = Incidence of Meningococcal Disease among the population aged over 15 years; Square = Incidence of Meningococcal Disease among children aged 0-14 years; Diamond = Incidence of Meningococcal Disease among the total population.

large [8]. Thus, children under 14 years in Ukraine are at a major risk for MI infection, and mortality rates account for 78.35% (**Figure 7**). Altogether, there is a strong direct relationship of MI incidence among age groups that exactly fit the local pyramid of age.

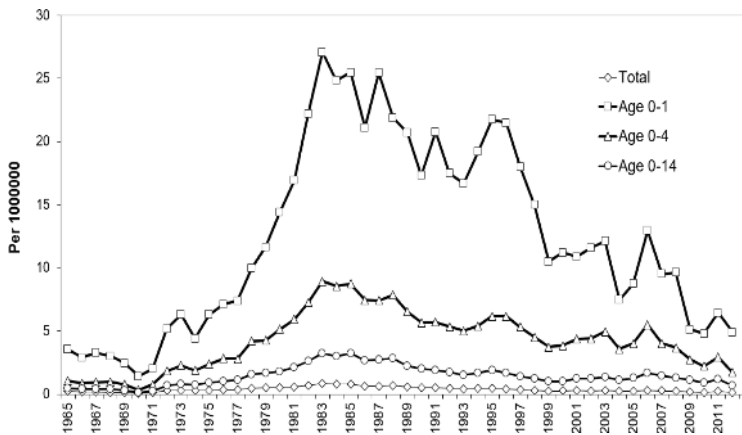


Figure 7. Mortality of meningococcal infectious disease among you children by class of age (Ukraine, 1965–2012). Legend: Legend: Abscissa = time (year); Ordinate = person with meningococcal infection per 100,000 people by age class; Empty circle = Incidence of Meningococcal Disease among children aged 0-14 years; Square = Incidence of Meningococcal Disease among children aged 0-1 years; Diamond = Incidence of Meningococcal Disease among the total population; Triangle = Incidence of Meningococcal Disease among children aged 0-4 years.

The correlation coefficient between the total number of cases of MI and the number of population for the years was $r = 0.9676$ (1990–2014). The correlation coefficient between the overall incidence and the total population was $r = 0.9556$ (Figure 8).

The correlation coefficient between number of the MI cases among children 0–14 years of age and number of children was of 0.9531. The correlation coefficient between the MI incidence among children 0–14 years of age and number of children was of 0.8163. The correlation coefficient between the total incidence of MI and the number of children was 0.9239. The correlation coefficient between the total number of cases of MI and the number of children was 0.9420.

All of the above present a direct and strong statistical correlation between the dynamics of age structure, the population and the incidence of MI. Peak incidence and mortality of meningococcal disease occurred in Ukraine in the mid-80s, also corresponding to this time of national birth rates or a “baby boom.”

Children's age is an indirect risk factor for invasive meningococci disease (IMD), while youngest children are more susceptibility to the pathogen, including predisposing factor of IMD and high transmission risk among over-crowded communities (i.e., school, recreation area, etc.). Incidence may also be reduced when the relative number of children decreases, and the whole population is aging (as it is in Ukraine and Europe). Indeed, during the study period, the number of children relatively decreased by twofold among general population, while the total number of population also decreased in Ukraine. Thus, we believe that the incidence of IMD in different age groups defined different levels of susceptibility of the pathogen for these groups.

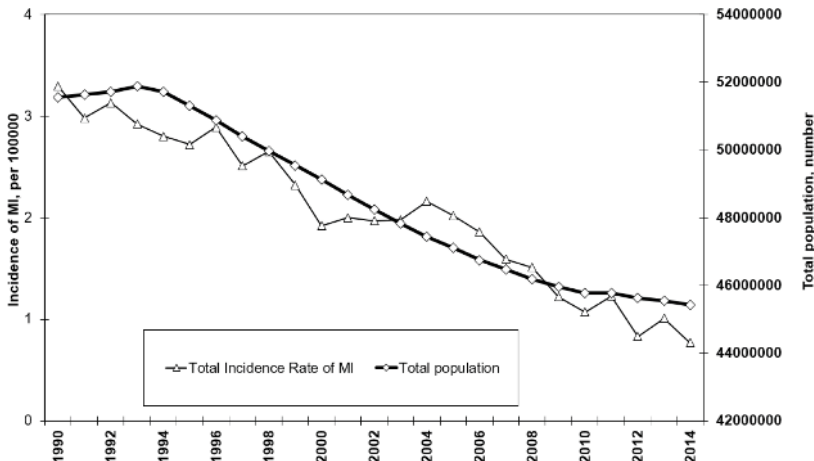


Figure 8. The dynamics of relationship between the overall incidence of meningococcal infection and the general population (Ukraine, 1990–2014). Legend: Abscissa = time (year); Ordinate = case of meningococcal infection per 100,000 people; Diamond = number of the total population; Triangle = Incidence of Meningococcal Disease among the total population.

3.6. Spatial rural as compared to urban distribution of meningococcal infection

In **Figure 9**, we see that the frequency of MI between cities and villages differ slightly. In cities, the total number and density of the population is greater than in the villages. This is evidenced by the result of ANOVA analysis of MI incidence for the period of 1990–2014 years for the urban and rural population of Ukraine. Estimated value of Fisher criterion (1.2) is less than the critical value (4.04). Thus, we have confirmed the statistical null hypothesis of no effect of residence on the incidence of MI.

These data may indicate that the percentage of the susceptible population in cities and towns are approximately equal. He also points to the sporadic incidence of MI in Ukraine.

3.7. Meningococcal carriage

Indeed, as a first factor in favor of such observations, one has to consider that meningococcus carriage is the most widespread form of meningococcal infection, that is, for one patient with IMD there is an estimate of more than thousands asymptomatic carriers of the pathogen. Carriage rates can range between 1 and 50% while varies with age, socioeconomic status, and connected with the predominant strain circulating in the area, and a number that appears not to vary with season or herd immunity. However, nasopharyngeal carriage surveillance is not recommended neither reported as a practical useful public health tool [9]. Also, data on nasopharyngeal carriage are available from state bacteriological laboratory in Ukraine (Ukrainian Centre for Disease Control and monitoring of the Ministry of Health of Ukraine) (**Figure 10**). Indeed, diagnostic tests are run annually by the Sanitary-epidemiological service

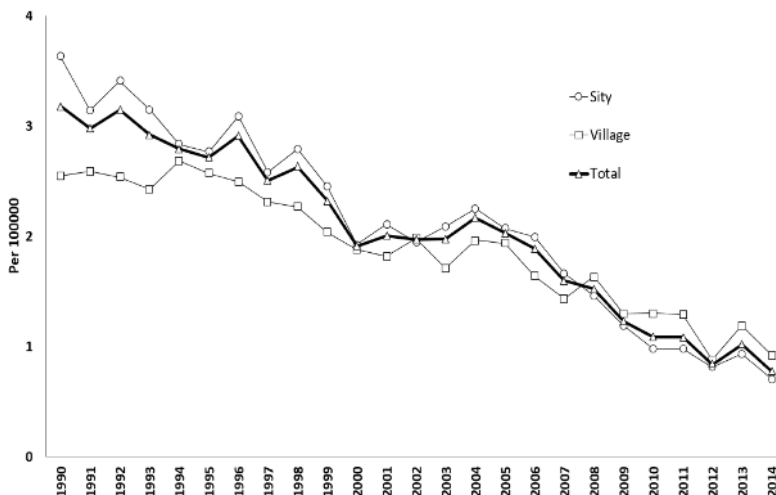


Figure 9. Dynamics of meningococcal infection in Ukraine in rural and urban areas (1990–2014). Legend: Abscissa = time (year); Ordinate = case of meningococcal infection per 100,000 people; Circle = Incidence of Meningococcal Disease in urban settings; Square = Incidence of Meningococcal Disease in rural; Triangle = Incidence of Meningococcal Disease among total population.

of Ukraine using nasopharyngeal swab. This approach was conducted in order to identify the level of circulating *N. meningitidis* in Ukraine among the healthy children and adolescents and also among all persons who had contact with MI patients, while contact persons represent all age groups or the general population. Such study was carried out in all 26 regions (oblasts) of Ukraine.

From 1992 to 2012, 890,061 people (average of 42,384/year) were investigated, moreover, 482,435 healthy people (average of 23,973/year) of all ages who have had contact with confirmed patients with MI, were also tested for meningococcal carriage in Ukraine. The results of these time series of MI carriers are shown in **Figure 9** and show the risk among healthy children and adolescents as an average of 0.99% as compared to 1.97% of the general population. Ultimately, such risk of infection is a factor of emergence of IMD and determines the level of prevalence of a small percentage of carriers is due to the large stratum of old adults and the low sensitivity of bacterial tests in Ukraine. The risk of infection is a necessary susceptibility factor for the emergence of IMI and therefore constantly determines the level of prevalence of meningococcal carriage.

3.8. Meningococcus serogroup distribution

In 1992–2012, information on the meningococcus serogroups was reported for 9484 IMD cases in Ukraine. The meningococcus B serogroup was responsible for 48.9% of IMD, followed by the meningococcus A serogroup (15.78%) and the meningococcus C serogroup (13.21%). The meningococcus D, X, Y, Z, 29E and W135 made up to 3.19% of IMD cases. Non-capsular strains represented 18.91%. During that same period, total information on serogroup was reported for 15,868 carriers. The meningococcus serogroup B was responsible for 36.15%



Figure 10. Meningococcal carriage dynamics among different population group survey in Ukraine (1992–2012). Legend: Abscissa = time (year); Ordinate = absolute number of carriers of meningococci; Circle = Prevalence (%) of meningococcal carriage among the healthy children and adolescents; Diamond = Prevalence (%) of meningococcal carriage among persons who had contact with MI patients (all age groups or the general population).

of carriers of meningococcal infections, followed by serogroup C (7.74%) and serogroup A (7.17%). The meningococcus serogroups D, X, Y, Z, 29E and W135 represented 6.75% of carriers' meningococcal infections the known serogroup. Not typed strain represented 42.19% of carriers of meningococcal infections (**Figure 11**).

In 2012, information on serogroup was reported for 3234 of confirmed IMD cases in EU countries including 68% of serogroup B, 17% of serogroup C (17%), and a total of 93% included B and C, Y [8]. It is clearly seen that in the EU and also in Ukraine IM case are due mostly to serogroup B, while serogroups B and C are less represented in Ukraine than in EU.

In 2008, serogroup C incidence of was 0.21 per 100,000 in Ukraine. In 2012, it dropped to 0.08 per 100,000. From 2008 to 2012, this index was slightly higher than the 0.1 per 100,000 in EU/EEA countries [9]. Thus, in the Ukraine, currently, the incidence of serogroup C is not different for EU/EEA but in Ukraine not carried out vaccination against Men C. This fact does not negate the benefits of vaccination but requires further detailed study. When one compares the incidence Men type C in EU with routine vaccination and Ukraine, where routine vaccination against MI has never been carried out, the effectiveness of Men C vaccination appears negligible because the incidence Men type C in EU and Ukraine is not different.

In Europe and Ukraine, decline in the incidence of other serogroups (A and B) was not the result of specific interventions. We believe that demographic situation in Ukraine population has decreased from 52 to 45 million over the past 25 years. Birth rate decreases, and therefore, child population falls, altogether this will certainly not contribute to an increase incidence of IMD in Ukraine for the coming decade. The introduction of routine vaccination of IMD in Ukraine requires careful study because there is limited funding for public health.

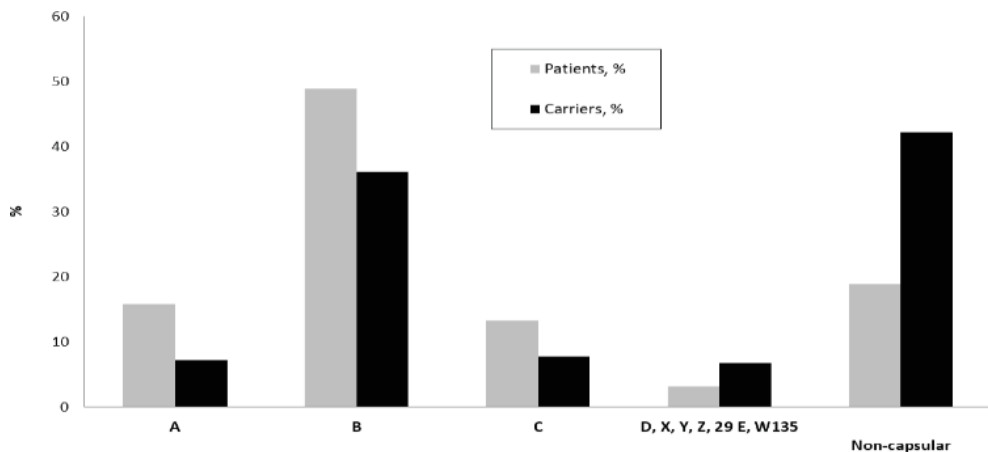


Figure 11. Distribution of meningococcus serogroups among patients with meningococcal disease (n = 9484) and healthy carriers of (n = 15,868), Ukraine, 1992-2012. Legend: Abscissa = Meningococcus serogroups; Ordinate = cases of meningococcal disease (%); red bar = healthy carriers of MI-pathogen (%); blue bar = patients with meningococcal disease (%).

4. Clinics

Among the 18,914 cases of IMD reported in Ukraine, 38.4% were meningococemia, 29.9% were meningococemia with meningitis, 27.9% meningitis and others 2.8% were of different minor etiologies. Other clinical forms have not been also clearly recognized and characterized as pneumonia or mixed clinical forms.

Also, the distribution of clinical forms of IMD in Ukraine is very different from the one observed in the EU countries in which meningitis prevails for 43.0%. Meningococemia and meningococemia with meningitis represent, respectively, 21.0 and 29.0% of total IMD in the EU [10].

Case fatality rate (CFR) of Meningococcal disease in Ukraine for the period considered (1992–2012) was of: 12.1% for IMD (n = 18,914); 18.9% for Meningococemia (n = 7448); 10.1% for Meningococemia (n = 5660); 5.94% of Meningitis (n = 5273); and 5.6% for others undefined clinical forms (n = 538).

In 2012, overall CFR in EU/EEA countries was 7.9%, (3185 confirmed IMD cases). The highest CFR reported (n = 1563) among cases presenting septicemia was 18.8%, followed by cases meningitis with septicemia of 11.1%, and then by cases with meningitis (3.7%) [11]. In Ukraine, the higher observed overall CFR of IMD greater than in the EU can be attributed to the frequency of septicemia.

Meningococcal disease CFR among children in Ukraine during the period of 2010–2015 ranged from 14.7 to 19.1% occurring as follows with respect to the age class: first year of life, 66%; 1–3-year old, 30%; over three-year old, 4%. Among 77% of patient death occurred during the first 24 h after onset.

According to the children's infectious hospital of Kiev, for the past 15 years, serotypes prevail as follows: meningococcal serogroup B, 57%; serogroup A, 19%; serogroup C, 20%; and other serogroup, 4%. Meningococemia was diagnosed in 47% of patient with meningococemia, 41% meningitis, while 12–76% of children with meningococcal disease had a complicated course of the disease, including septic shock, brain edema, multiple organ failure, disseminated intravascular coagulation syndrome, among others.

5. Multiple linear regression model

From this data set and temporal series, some tentative models were developed for a better understanding to the disease dynamics. Assuming that the proportion of susceptible individuals is a constant value a reported to a large population (eventually of genetic origin), this could explain the main feature of the epidemic process of meningococcal disease and ecological characteristics of meningococcus commensality.

Also, meningococcus as a species may exist as a non-pathogenic microorganism. IMD will then arise only among susceptible people who have a genetic predisposition while in any large population, such a percentage is very small (<1%).

In order to calculate the percentage of susceptible population to IMD, it is possible to calculate it as a risk of susceptibility (RS), the percentage of susceptible, i.e. approximate proportion of the population susceptible" (APPS) to IMD. In order to calculate APPS, we first calculate the annual estimated number of carriers, AAQC (infected people without clinical manifestations):

$$APPS = (IMD\ number:AAQC) \times 100\% \quad (1)$$

where AAQC = annual approximate quantity of carriers (infected people without clinical manifestations); CPR = carrier prevalence rate (from the ratio of the carriers detected among people examinees); N = the census of the population of the studied territory; 365 = days (i.e., a year); D = average duration of carriage status (not detected after 14 days).

where AAQC formula is derived from PR formula:

$$AAQC = \frac{CPR \times N \times 365}{D} \quad (2)$$

where PR = prevalence rate; IR = incidence rate; D = average day duration for one case of carriage [12].

Ultimately, AAQC formula allows to convert the data of sample surveys (i.e., prevalence of meningococcal carriage showed (**Figure 9**) to indicators of incidence (or the annual approximate number of carriers). Thus, we calculated the AAQC among healthy children for the period 1992–2012 years. The AAQC of children was calculated from 2,206,475 persons. The proportion of IMD cases (i.e., % susceptible) presented an average of 0.0360% ± 0.0189, that is: in overall, one IMD patient associated with 5271 carriers in during 1990–2012.

Moreover, this way we calculated indicators for period of time from 1992 to 2012 for the general population. The annual average number of carriers in the general healthy population was 24,990,502 persons (variation of 15,480,263–34,746,741 per year). The proportion of IMD cases (i.e., % susceptible) had an average of 0.0036% (0.0022–0.0058% per year), that is: one IMB patient associated an average of 29,729 carriers.

In overall, this is consistent with the fact that the IMD incidence among children exceeds IMD incidence in the general population (or adult) by 10-fold or more.

The total risk of disease (RD) is expressed as a product of risk of infection (RI) to risk of susceptibility (RS) where $RD = RI \times RS$. Thus, in our paradigm, RS and RI are the final and necessary causes of IMD emergence and spread to human population. All other causes that may affect IMD incidence will act indirectly through RI and RS.

Therefore, we built multiple regression models of the epidemic process of MI, where the incidence of IMD is the dependent variable, while independent variables are the level of meningococcal carriage (RI) and the proportion of the susceptible population (RS). The construct of the regression model was by deriving multiple regression method [12]. Multiple linear regression models of IMD in Ukraine were therefore developed [13]. We used for the model the data presented in the figures 6 and 10.

Our first model takes the following form of the regression equation:

$$Y_1 = -7.43 + 8.26 X_1 + 227.63 X_2, \quad (3)$$

where Y_1 = IMD incidence per 100,000 children 0–14 years; -7.43 (or “ a ”) = constant, which corresponds to the mathematical expectation X_1 and X_2 if $Y = 0$; X_1 = prevalence of carriage among healthy children aged 0–14 (%); X_2 = approximate proportion of the population susceptible to the IMD among children aged 0–14, or APPS (%); 8.26 (or “ b_1 ”) = regression coefficient showing the change of level Y , if X_1 is changed to 1%; 227.63 (or “ b_2 ”) = regression coefficient showing the change of level Y , if X_2 is changed to 1%.

Note that the influence of the regression coefficients (b_1 and b_2) and constant “ a ” at incidence Y is statistically significant (Student exact test: $b_1 = 14.56$ with $p = 2.13 \times 10^{-11}$; $b_2 = 15.39$ with $p = 8.38 \times 10^{-12}$; $a = 7.54$ with $p = 5.59 \times 10^{-7}$).

In the model, the coefficient of multiple correlation $R = 0.9697$ and its standard error is equal to 0.5069 ($R^2 = 0.9404$, i.e. 94.04%) that statistically significance explains IMD incidence and shows the high descriptive properties of the model. Ultimately, this model appears highly significant (Fisher’s exact test = 142.04 $p < 0.05$ at 95% confidence) describing the totality of the properties of the epidemic process of MD among children aged 0–14. Analysis of the residuals values of the model did not find any autocorrelation. Overall, the model encompasses all properties and is statistically significant.

Our second model takes the following form of the regression equation:

$$Y_2 = -1.59 + 0.89 X_1 + 469.13 X_2, \quad (4)$$

where Y_2 = IMD incidence per 100,000 population; X_1 = prevalence of carriage among persons who had contact with IMD patients (or among total population), %; X_2 = approximate proportion of the population susceptible to the IMD among total population, APPSIMD, %. The model has excellent descriptive properties and statistically significant. The coefficient of multiple correlation $r = 0.9937$ and its standard error is equal to 0.0645 , accordingly with $r^2 = 0.9875$. Residuals analysis of the model did not find any autocorrelation (i.e., almost normal distribution.)

Model limitation: Our models use aggregated data form a survey, and therefore, our model does not allow for an adequate formal residual analysis. In order to perform such type of analysis, it requires to build at least 50 times of such models from necessary data sets. Also, our models do not take into account the potential heterogeneity of the pathogen.

6. Conclusion

Altogether the present and past surveillance of bacterial meningitis in Ukraine provide a unique source for a comprehensive understanding of the disease dynamics and, most importantly, allow to develop tools and strategies for control and prevention.

Thus, the results of mathematical modeling of IMD using the available time series of data suggest that the nature of the main manifestations of the epidemic caused by the MI process demonstrates the prevalence of meningococcal carriage and provides a measure of the of susceptible populations, which are both factors strongly associated and allow the assessment of immediate risk of IMD in country. The proposed multiple linear regression model of epidemic process of meningococcal disease will improve epidemiological surveillance of the disease. Moreover, such models will provide a strong mean for assessing the quality of vaccination against invasive bacterial infections as well as diphtheria.

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