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Varicella infection in a non-universally vaccinated population: Actual epidemiology in Bulgaria (2013–2015)

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ABSTRACT

Background: Varicella is a common and usually mild disease but it has great importance in regard to general infectious morbidity. The current study aimed to characterize possible risk factors of varicella epidemiology in Bulgaria, a country where infection follows its natural epidemiological pattern as no mandatory or recommended vaccine is currently applied.
Methods: Administrative regions of Bulgaria were used as units of observation and a set of sociodemographic and economic determinants, as well as geographic location (south or north) were tested for associations with the mean 3-year varicella incidence rates (2013–2015).
Results: The proportion of urban population, proportion of females, number of health care units and proportion of urban population aged <10 years were the four sociodemographic variables most strongly and significantly correlated ($p < 0.05$) with varicella frequency (Spearman's rank correlation coefficients of 0.62, 0.47, 0.43, and 0.38, respectively). After reducing the number of intercorrelated factors to a few principal components and accounting for confounders, the demographic component and geographic location remained most robustly associated with varicella incidence in Bulgaria (adjusted R^2 of 0.51, $p < 0.001$).
Conclusions: The results obtained identify important determinants in the local epidemiology of varicella and show that community characteristics should be considered, to improve our understanding of varicella distribution.

Introduction

Varicella (chickenpox) is a common communicable disease that is endemic in all geographic areas of the world. It is usually a childhood infection, as the majority of the cases occur in people younger than 6 years [1]. The disease manifests as a mild skin rash but complications are possible and more frequent in newborns, elderly adults, pregnant women and immunocompromised individuals. Although rare, fatal cases also exist and represent 0.01%–5.4% of hospitalized varicella patients in Europe [1].

Various socio-demographic, economic and environmental factors influence varicella incidence in different climatic and geographic regions. Environmental temperature [2], epidemiological interference with other viruses [3] and rural residence [4] are the most important in tropical regions whereas inequalities in wealth, infant vaccination coverage and child care attendance remain most significant in Europe [5].

Varicella is a vaccine-preventable disease and the World Health Organization advises routine childhood immunization in countries with a significant public health impact of the disease [6]. Some countries (e.g., the United States, Latvia and Greece) have adopted universal immunization against varicella whereas others like Bulgaria have no specific recommendations in place. Despite the leading position of varicella in the infectious morbidity of Bulgaria [7] and mandatory notification of the disease, the question of routine immunization has never raised for public discussion and vaccines against varicella, as well as guidance for their application, are unavailable.

Different vaccination policies around the world determine the presence of areas where varicella infection is more or less controlled and the epidemiology has largely shifted towards very low infant incidence [8], as well as countries where chickenpox follows its natural epidemiological pattern with almost all children under 10 years infected with the virus [9]. Accordingly, most recent studies have assessed the benefits of varicella vaccination by comparing the epidemiology before and after implementation of immunization, and seroprevalence studies have used samples from

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Table 1
Annual incidence rates (per 100,000) and mean 3-year rates of varicella in regions of Bulgaria.

	2013	2014	2015	Mean 3-year
Southern regions				
Blagoevgrad	168.2	161.3	262.8	197.1
Burgas	228.5	175.5	171.3	191.8
Kardzhali	114.9	452.5	29.1	199.3
Kyustendil	496.5	53.9	131.7	229.5
Pazardzhik	205.4	96.4	190.4	164.1
Pernik	1000.0	129.1	323.6	487.1
Plovdiv	357.1	412.4	559.1	442.6
Sliven	228.4	388.8	307.0	307.9
Smolyan	308.9	524.6	112.0	316.6
Sofia City	864.8	360.0	502.4	575.2
Sofia Province	331.7	202.1	180.5	238.5
Stara Zagora	487.0	399.1	330.9	406.0
Haskovo	473.0	331.6	409.1	404.7
Yambol	320.0	360.3	428.0	369.0
Northern regions				
Varna	1009.8	357.1	585.9	663.9
Veliko Tarnovo	675.3	171.1	156.7	336.6
Vidin	324.7	296.7	567.8	394.6
Vratsa	237.7	351.1	164.0	251.3
Gabrovo	710.2	465.0	273.9	485.5
Dobrich	518.7	300.3	241.4	354.5
Lovech	177.0	955.7	117.9	417.1
Montana	804.4	423.4	191.0	476.2
Pleven	858.3	202.9	195.7	422.1
Razgrad	410.5	384.7	407.7	401.0
Ruse	461.7	334.7	408.6	401.8
Silistra	255.1	60.2	143.9	153.5
Targovishte	259.9	426.0	352.4	345.8
Shumen	625.6	270.7	243.6	380.8
Total	531.6	319.8	346.1	399.8

Table 2
Spearman's rank correlation coefficients between potential risk factors and mean 3-year varicella incidence (2013–2015) in Bulgaria.

Factor	Spearman's rank correlation coefficients (p-value)		
	All regions	Southern	Northern
Average annual population[a,e]	0.12 (0.54)	0.06 (0.84)	0.24 (0.41)
Population density (persons per km^2)[a,e]	0.31 (0.11)	0.28 (0.33)	0.29 (0.31)
Proportion of women (%)[a]	**0.47 (0.01)**	**0.58 (0.03)**	0.32 (0.26)
Proportion of urban population (%)[a]	**0.62 (0.001)**	**0.61 (0.02)**	**0.59 (0.03)**
Proportion of persons declaring Bulgarian ethnicity (%)[b,e]	0.34 (0.08)	0.42 (0.14)	0.28 (0.33)
Proportion of persons declaring Roma ethnicity (%)[b]	−0.20 (0.32)	−0.17 (0.56)	−0.31 (0.27)
Proportion of population aged <10 years (%)[a]	−0.14 (0.49)	−0.24 (0.42)	−0.04 (0.89)
Proportion of urban population aged <10years (%)[a]	**0.38 (0.04)**	0.43 (0.12)	**0.56 (0.04)**
Proportion of children in day care units aged 3–6 years (%)[a]	0.18 (0.36)	0.13 (0.66)	0.24 (0.40)
Number of health care units per 10,000 persons[a]	**0.43 (0.02)**	**0.81 (0.001)**	0.16 (0.59)
Population per physician[a]	−0.36 (0.06)	−0.07 (0.81)	**−0.60 (0.03)**
Incidence of other nationally notifiable infectious diseases[c]	0.06 (0.76)	0 (1.00)	0.28 (0.33)
Migration increase (%)[a]	0.26 (0.18)	0.20 (0.48)	0.20 (0.49)
Unemployment (% of economically active population)[a]	−0.31 (0.10)	0.02 (0.95)	**−0.67 (0.01)**
Economically active population (%)[a]	0.13 (0.50)	0 (1.00)	0.44 (0.12)
Inequality of income distribution (ratio of 20% lowest and 20% highest incomes)[d,e]	−0.26 (0.19)	−0.32 (0.27)	−0.36 (0.21)
GDP per capita (BGN)[d,e]	0.30 (0.12)	0.20 (0.48)	0.34 (0.23)

Statistically significant correlation coefficients ($p < 0.05$) are given in bold.
[a] NSI mean 3-year estimate (2013–2015).
[b] NSI last national census (2011) data.
[c] NCPHA data.
[d] NSI estimate for 2014.
[e] Non-normally distributed variables.

certain populations (non-immune migrants [10], pregnant women [11,12] or health care workers [13]) as the unit of analysis. Other studies have compared incidence rates and their corresponding risk factors at international level, but no single model of varicella transmissibility has been developed, even for neighboring European countries [5,9], which differ in age-related social behaviors as well as in surveillance systems [14] and vaccination policies. Although useful in some respects, the abovementioned approaches cannot address the actual community-level factors responsible for varicella transmission and local distribution. To characterize the sociodemographic and economic correlates of varicella incidence, the present study adopted a different approach, namely, description of possible risk factors associated with varicella frequency in a "vaccine-free" country (Bulgaria) and use of administrative regions as units of observation, to thereby benefit from an identical system of notification and distinct community determinants.

Materials and methods

Bulgaria is a country in southeast Europe with a total population of 7,153,784 (as of 31 December 2015). Its territorial and administrative structure consists of 28 regions (listed in Table 1) with populations ranging from 91,235 (Vidin) to 1,319,804 (Sofia City).

Varicella is a nationally notifiable infectious disease with a well-established case-based system of notification; any medical unit must report the case to the corresponding regional health inspectorate within 24 h after detection. The regional inspectorates summarize the data on a daily basis for submission to the responsible national body, the National Centre of Public Health and Analyses (NCPHA). Three types of cases are reported: possible (any person meeting the clinical criteria, listed in Regulation 21/18.07.2005), probable (any person meeting the clinical criteria and with an epidemiological link) and confirmed (any person meeting the clinical and laboratory criteria).

For the present study, data on varicella cases for 2013–2015 were derived from the public databases of the NCPHA [15] and the National Centre of Infectious and Parasitic Diseases [16], and data on population number were from the National Statistical Institute (NSI) database [17], respectively. Incidence rates at national and regional level were calculated using the number of reported new varicella cases (possible, probable, and confirmed) during 2013, 2014 or 2015 as the numerator and the official annual estimates for the total population number in each region for the corresponding year as the denominator. The resulting figures were multiplied by 100,000 to present the incidence as an annual rate per 100,000 inhabitants. The mean 3-year incidence was calculated by dividing the total number of cases for 2013–2015 by the total number of person-years of observation and multiplying the result by 100,000.

A set of regional sociodemographic and economic characteristics (all obtained from the NSI database) were used as continuous variables to test for correlation. For most of them (Table 2), the mean 3-year statistical estimate was considered; where it was not possible to obtain the mean estimate, either the 2014 estimate or 2011 census data were used. To test the possible association between varicella incidence rates and the set of selected variables, the Spearman's rank correlation coefficients were calculated using R Commander software [18], with a significance of $p < 0.05$. As some of the studied variables were intercorrelated, principal component analysis was applied to reduce the number of variables and to create linearly uncorrelated combinations of factors. Each gener-

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