Newly introduced vaccines: effectiveness and determinants of acceptance

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Chapter 2.1 Seasonal influenza in 48 countries of the WHO European Region: analysis of influenza surveillance data from 2008/2009 to 2012/2013

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Abstract

Background Better understanding of different influenza metrics in the WHO European Region and subregions will support influenza related policy and preparedness decisions. We therefore assessed different metrics of five consecutive influenza seasons in the Region and subregions.

Methods The data were derived from the WHO European Influenza Surveillance Platform (EuroFlu) that contains data on clinical and laboratory-confirmed influenza from 48 WHO European Region Member States. We estimated influenza seasons' length and standard deviation (SD) in weeks, median influenza peak week and interquartile range (IQR), and spread (R^2). A p-value of <0.05 from one-way ANOVA and nonparametric median test was considered as statistically significant.

Results Length of the seasonal influenza was similar in the countries throughout the Region and lasted about 8.9 weeks (SD 3.59). There was strong to moderate west to east spread. Seasonal influenza peaks were different across the Region: it first peaked in week 5 in northern and western Europe and central Asia, and peaked last in eastern Europe in week 8.

Discussion From 2008/2009 to 2012/2013, we found that seasonal influenza length was similar across the Region, but it was rather diverse in its timing. There was also evidence of west to east spread of influenza. This should be taken into account for influenza preparedness in the Region.

Introduction

Influenza is a respiratory disease responsible for substantial increase in morbidity, mortality and costs during seasonal epidemics and pandemics [1][2]. Better understanding of the epidemiology of influenza is necessary for planning public health interventions and preparing for the upcoming epidemics and pandemics. Different metrics, such as timing, duration and spread of influenza can be used to describe influenza seasons, to set the optimal time for the influenza vaccination campaigns or to predict the impact of the influenza season.

Despite that influenza peaks in temperate climates are documented to occur during the winter season, the seasonality of influenza in general still lacks sound scientific explanation [3][4]. Only few studies described influenza seasons by exploring the differences across different countries, regions or continents during multiple years [5][6][7]; one study assessed the differences between seasonal and A(H1N1)pdm09 pandemic influenza seasons [8]. Although some of these studies included European countries [6][8], only one study actually assessed influenza season characteristics in the WHO European Region [8]. Still, this study was conducted to compare the pandemic A(H1N1)pdm09 and seasonal influenza, and did not focus on (sub)regional analysis with regard to different metrics of influenza seasons. To provide further evidence about the potential diversity of influenza seasons in this Region, we estimated several metrics of influenza seasons, namely timing of the peak of influenza activity, the start, the end, the length, and the spread of influenza seasons in the Region and its subregions.

Methods

We used the data collected on the WHO European Influenza Surveillance Platform (EuroFlu) euroflu.org, which contains influenza surveillance data from 48 out of 53 WHO European Region Member States. The Region covers the population of 896 million inhabitants constituting a unique data set (http://www.euroflu.org/). Additionally, sub-national data from the United Kingdom (Northern Ireland, Scotland, Wales, England) and the Russian Federation (Central, Far Eastern, North-western, Siberian, Southern, Urals and Volga regions of the Russian Federation) were extracted. European Union and

European Economic Area (EU/EEA) Member States participate in the European Influenza Surveillance Network (EISN) coordinated by the European Centre for Disease Prevention and Control (ECDC) (http://ecdc.europa.eu/en/activities/surveillance/eisn/Pages/index.aspx) and report data to the ECDC surveillance platform TESSy (http://ecdc.europa.eu/en/activities/surveillance/TESSy/Pages/TESSy.aspx) with real-time transfer of data to EuroFlu. The historic influenza period in Europe is winter, so between weeks 40 to 20 influenza surveillance data is collected weekly. The data is collected via influenza surveillance networks based on sentinel or universal surveillance models. Sentinel networks provide data on influenza collected from a stable sample of general practitioners; the important feature of this data source is that it is representative for the general population and the denominator is known [9]. There is a sampling strategy which aims to be representative of the population under surveillance. Countries conducting universal surveillance register all cases of acute respiratory infection (ARI) or influenza-like illness (ILI) at all health care facilities in the country and sampling is by convenience according to the judgement of the clinician. Our study included data collected from 2008-2009 through 2012-2013 influenza seasons. Due to its different timing, the 2009-2010 pandemic influenza season was excluded from the pooled seasonal influenza seasons' analysis. Countries were included in the analysis when the weekly laboratory-confirmed influenza or ILI and/or ARI were reported for at least 20 consecutive weeks, allowing one week of missing data at any time. Although slightly different definitions of ILI and ARI are used in different countries [10], generally ILI was defined as sudden onset of at least one respiratory (cough, sore throat, shortness of breath) and systemic (fever or feverishness, malaise, headache, myalgia) symptoms, and ARI was defined as sudden onset of at least one respiratory symptom (cough, sore throat, shortness of breath, coryza) symptom and clinician's judgement that the illness is due to an infection (http://ecdc.europa.eu/en/activities/surveillance/eisn/surveillance/pages/influenza_case_definitions.aspx).

The influenza activity peak week was defined as a week of the highest laboratory-confirmed influenza positivity and ILI/ARI rates for each country/sub-national area. If more than one peak was observed, the influenza peak with the highest number of influenza cases was chosen. It was estimated as a week with the highest proportion of the reported laboratory-confirmed cases from the total collected specimens that week and a week with the highest ILI/ARI rates from the population served by universal surveillance. The median influenza peak activity weeks from virological and clinical data and their interquartile ranges (IQR) were calculated. We estimated the match between the virological and clinical peaks by calculating the difference between the peaking weeks, and we expressed the amount of matching peak weeks in percentage.

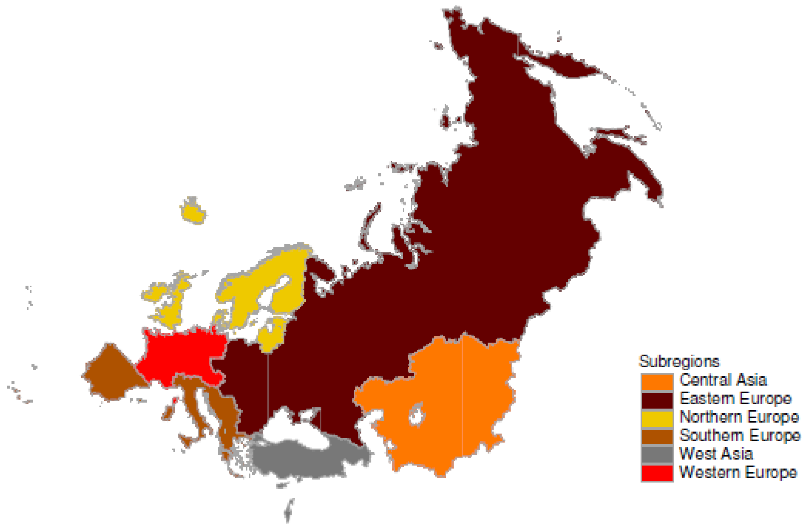
The length of the influenza seasons was calculated using virological data, by subtracting the earliest week from the latest week in which at least 5% of the registered laboratory-confirmed influenza positive cases occurred between week 40 and week 20 [11]. The average season length and its standard deviation were calculated.

To assess the spread, we correlated the weeks of influenza peak activity of the laboratory-confirmed influenza and ILI/ARI incidence with the longitude of the middle of the country to assess west to east spread. We correlated the weeks of influenza peak activity with the latitude of the middle of the country to assess the south to north spread. Pearson's correlation coefficient was considered as significant when p-value $<=0.05$; the correlation was defined as very strong ($r>= 0.70$), strong (0.40 to 0.69), moderate (0.30 to 0.39), weak (0.20 to 0.29) or negligible (0.01 to 0.19).

The dominance of influenza virus (sub)type was assessed for countries that reported the number of influenza cases. The threshold for dominance was set at 60% and the threshold for co-dominance was set at 40%/60% [12][13]. The following categories were used to stratify the analysis by influenza type: influenza A, influenza B and co-dominant influenza A and B. The following categories were used to stratify the analysis by influenza A subtypes: seasonal A(H1N1), A(H3N2), A(H1N1)pdm09 pandemic strain, co-dominant seasonal A(H1N1) and A(H3N2), co-dominant seasonal A(H1N1) and A(H1N1)pdm09 pandemic strain and co-dominant A(H1N1)pdm09 pandemic strain and A(H3N2).

To assess whether influenza metrics vary across geographical areas and influenza seasons, the laboratory-confirmed influenza peak week activity, length, and spread were estimated for the Region, across the subregions and different influenza seasons, and stratified based on the United Nations (UN) countries' geographical classification [14], also see Figure 1. Based on the UN classification, the Region was categorized into six subregions, and included central and western Asia and eastern, northern, southern and western Europe.

Figure 1. Subregions of the WHO European Region.



To compare the medians of influenza peak activity weeks and the medians of the four seasonal influenza years mean lengths across the subregions and influenza types we used nonparametric median test (p-value >=0.05 indicating no differences across the medians). The mean length of influenza seasons in different years, when stratified by the subregions and influenza (sub)types was compared by one-way ANOVA (p-value <0.05 indicating significant difference across the means). The difference between the mean lengths of seasonal influenza and pandemic influenza was tested by independent t-test (p-value <0.05 indicating significant difference). Statistical analysis was performed with SPSS 20.0.0.2.

Results

The number of countries/sub-national areas that reported laboratory-confirmed influenza and/or ILI/ARI is presented in Appendix 1. Throughout the years, approximately 49, 36 and 28 countries reported virological, ILI and ARI surveillance data respectively; the number of countries reporting their surveillance data slightly increased over the years. During the seasonal influenza years (excluding the pandemic season of 2009/2010), the within-year agreement between the virological influenza peak activity week and clinical influenza peak activity week with no more than one and two weeks difference was 54.8% and 72.1% respectively (Table 1). When we limited the analysis to EU/EEA countries, the agreement was slightly higher, 61.6% and 77.2% (Table 1). Similar patterns in agreement between the virological and clinical influenza peak weeks were found during the pandemic season in 2009/2010. Strong agreement between the virological and clinical data with at least two weeks difference indicates that any of the two might be used when describing influenza seasons. For this reason the remainder of our calculation is based on laboratory-confirmed peak activity.

Table 1. The agreement between the influenza activity peak weeks based on virological and clinical data in the WHO European Region and EU/EEA.

	2008/2009	2009/2010	2010/2011	2011/2012	2012/2013	Overall match during the seasonal years (excluding 2009/20010 season)
WHO European Region						
At most 1 week difference	67.7%	54.8%	54.8%	45.7%	51%	54.8%
At most 2 weeks difference	77.4%	71.4%	81%	56.5%	73.5%	72.1%
EU/EEA						
At most 1 week difference	66.7%	66.7%	62.5%	57.7%	59.3%	61.6%
At most 2 weeks difference	75%	87.5%	79.2%	69.2%	85.2%	77.2%

EU/EEA: European Union/European Economic Area.

In the WHO European Region during the 2008/2009 to 2012/2013, seasonal influenza activity based on laboratory- confirmed influenza usually peaks between weeks 4 and 9 (Table 2). Subregional analysis showed that when taking all four seasonal influenza years together, seasonal influenza usually first peaks in northern and western Europe and central Asia in week 5, and peaks later in eastern Europe in week 8 (Table 3). The nonparametric median test also revealed that there were subregional differences in timing of the influenza peak (p-value for all the four seasonal influenza years < 0.05).

Table 2. Influenza peak activity, length, and spread based on the laboratory-confirmed influenza between 2008/2009 and 2012/2013.

Season	N	Peak activity week (IQR)	Length in weeks (SD)	W-E (R^2)	S-N (R^2)
2008/2009	38	4 (3-9)	8.42 (4.42)	0.69**	-0.16
2009/2010	50	47 (46-48)	7.56 (4.13)	0.33*	0.02
2010/2011	47	4 (3-7)	8.96 (3.43)	0.37*	-0.14
2011/2012	52	9 (6-11)	8.75 (4.12)	0.10	0.33*
2012/2013	54	6.5 (5-9)	9.59 (2.40)	0.31*	-0.15

IQR: interquartile range; SD: standard deviation; R^2: Pearson's correlation coefficient; W-E: west to east spread; S-N: south to north spread; *p-value <0.05; **p-value <0.01.

Based on virological data, the average length of seasonal influenza was 8.9 weeks (SD 3.6), but not statistically different across the subregions and different years (p-value resulting from one-way ANOVA >=0.05). Although the length of influenza seasons dominated by influenza type B were slightly longer (median 9.4 weeks) than the seasons dominated by influenza A (median 9.0 weeks) or codominated by influenza types A and B (median 8.1 weeks), no statistically significant differences in the length of influenza seasons (co)dominated by different types of influenza in the seasonal years was observed (p-value resulting from one-way ANOVA >=0.05). The dominating subtypes of influenza A in 2008/2009, 2009/2010, 2010/2011, 2011/2012 and 2012/2013 seasons were A(H3N2) (93.3% of the 28 countries/sub-national areas), A(H1N1)pdm09 (98.1% of the 52 countries/sub-national areas), A(H1N1)pdm09 (100% of the 46 countries/sub-national areas), A(H3N2) (in 96.1% of the 51 countries/sub-national areas) and A(H1N1)pdm09 (in 64.8% of the 54 countries/sub-national areas) respectively.

Table 3. Influenza peak activity, length, and spread based on laboratory-confirmed influenza by subregion across the seasonal influenza seasons of 2008/2009 and 2010/2011-2012/2013.

	Median peak activity week across 4 seasonal influenza seasons (IQR)	Mean length in weeks (SD)	W-E (R^2)	S-N (R^2)
Central Asia (n=4)	5 (4-9)	9.00 (2.60)	-0.22	0.97*
Western Asia (n=5)	7 (5-12)	9.27 (4.15)	0.91*	0.57
Eastern Europe (n=16)	8 (5-10)	9.67 (4.5)	0.43	-0.09
Northern Europe (n=13)	5 (3-8)	9.46 (3.68)	0.42	-0.02
Southern Europe (n=12)	7 (4-10)	8.15 (2.86)	0.55	0.06
Western Europe (n=7)	5 (4-6)	7.79 (1.52)	0.62	-0.63

IQR: interquartile range; SD: standard deviation; R^2: Pearson's correlation coefficient; W-E: west to east spread; S-N: south to north spread; *p-value <0.05; **p-value <0.01.

Influenza spread from west to east and from south to north was assessed by correlating the longitudes and the latitudes with the weeks of highest influenza activity (see Table 2&3). Based on the virological data, there was moderate to strong correlation between the longitude and influenza peak activity week indicating west to east spread in 2008/2009, 2010/2011 and 2012/2013 influenza seasons, and moderate correlation between the latitude and the peak activity week indicating south to north spread only in 2011/2012 season. After stratifying the analysis by subregion and correlating the longitudes and latitudes with the median influenza peak activity weeks across the four seasonal influenza years, no patterns of spread were detected in western, eastern, southern and northern Europe. There were very strong west to east and south to north spread patterns in western and central Asia respectively.

In EU/EEA countries there was very strong and strong west to east spread during 2008/2009 (r=0.77) and 2010/2011 (r= 0.65) influenza seasons respectively.

Pandemic influenza season in 2009/2010

During the pandemic, influenza peaked in week 47 and, similar to seasonal influenza years (independent t-test p-value >=0.05), it lasted about 7.5 weeks. There were no (sub)regional differences in its length, and there was evidence for moderate west to east spread. In EU/EEA countries there was strong west to east spread in 2009/2010 seasons (r=0.55).

Discussion

This study aimed to describe seasonal influenza season in the WHO European Region using metrics such as influenza peak activity week, the length of the season, and the spread. The study also aimed to assess whether these metrics were different by influenza types and subregions. We used the influenza surveillance data from the last five years; the analysis of seasonal influenza metrics was performed on four seasons excluding the 2009/2010 pandemic year. We found that the average seasonal influenza in the Region lasted about 9 weeks with no differences by subregion or influenza type. Influenza seasons first peak in western, northern Europe and in central Asia in week 5, and last in eastern Europe in week 8. There was indication of west to east spread and south to north spread in the Region. After stratifying by subregion, there was west to east and south to north spread only in western and central Asia respectively.

We found that the agreement between laboratory-confirmed influenza and ILI/ARI peaks in the Region with not more than two weeks apart was 72.1%, and it was somewhat higher when we looked at EU and EEA countries only, 77.2%. These results are similar to the previous study, where the agreement between the laboratory-confirmed influenza and ILI or ARI in Europe with at most two weeks apart was found to be between 68% and 84% [6]. Although the agreement between parameters based on virological and clinical data in the Region is somewhat lower than in EU/EEA countries alone, combined ILI/ARI data could be used to describe influenza seasons. Although ILI and ARI outcome definitions vary across the countries, at least in western European countries they share common criteria [10]. Further studies are needed to assess the ARI and ILI definitions for the entire Region and evaluate the benefits of standardizing influenza surveillance across the Region. In addition to definitions, the agreement between the virological and clinical data might be affected by other respiratory pathogens that cause ARI or ILI symptoms as well as lower consultation rates at certain time periods not associated with influenza activity, such as the Christmas and New Year holiday period [6].

In our study we found that on average seasonal influenza lasted for about nine weeks, which was not statistically different across the subregions, years or influenza types. We calculated the length of influenza season for every country by subtracting the earliest week with at least 5% of all laboratory-confirmed influenza cases from the latest week with 5% of all laboratory-confirmed influenza cases between week 40 and week 20. In a previous study, the average length of influenza season of 15 weeks was found, but this estimate reflects the length of influenza for the entire EISN region and not the average of the countries' estimates [6]. Due to different methods that have been used to calculate the length of influenza seasons the latter and our estimates cannot be directly compared.

We found moderate and strong west to east spread in all the seasonal influenza years except for 2011/2012, and we found moderate south to north spread in 2011/2012. To assess whether influenza metrics are diverse across the Region, we performed the analysis stratified by UN geographical subregions. There were strong west to east and south to north spread patterns in western and central Asia respectively. No significant spread patterns were detected in eastern, northern, southern and western Europe. In EU/EEA countries and the Region as a whole, our results showed similar influenza spread patterns to those previously reported indicating stronger west to east than south to north spread [6][8].

We also assessed the metrics of the 2009/2010 pandemic influenza season. Due to its different timing (the median week of influenza peak activity being in week 47), pandemic year metrics were excluded from the pooled analysis of seasonal influenza seasons. However, based on the duration and spread patterns, 2009/2010 pandemic influenza season was similar to other (non-pandemic) influenza seasons.

A previous study reported that influenza A(H3N2) viruses seem to be seeded to Europe from east and Southeast Asia; possibly because of strong travel and trade connections [15]. Trade and travel connections could also explain why we detected west to east spread in the WHO European Region and earlier influenza peak activity in western Europe than in eastern Europe. Western part of the Region is probably better connected to east and Southeast Asia than eastern part of the Region, meaning that influenza is seeded to the eastern part of the Region from the western part of the Region. The absence of south to north spread pattern might be a result of poorer connection with east and Southeast Asia and/or southern and northern subregions not having strong connection. It is also difficult to explain why after stratifying the analysis by subregion we detected very strong west to east and south to north spread patterns in western and central Asia respectively, but not in other subregions. Mapping of the connections, i.e. frequency of flights, might therefore be helpful in further revealing and explaining influenza spread patterns in the Region.

This is one of the first studies to describe seasonal influenza at the regional level in the WHO European Region. We included data from approximately 50 countries and/or country sub-national areas, and we were able to stratify the analysis by subregion and influenza (sub)type. We performed the analysis of influenza seasons' metrics when using laboratory-confirmed influenza and we found that the agreement between the virological and the clinical data was relatively high. We showed that seasonal influenza in the Region typically lasted for about 9 weeks independent of the subregion or dominant influenza (sub)type. Influenza seasons in the Region were rather diverse with regard to their timing. There was moderate to strong west to east spread, but almost no south to north spread, except in the subregion of central Asia. These results might be used to strengthen public health action plans related to influenza preparedness, more precise allocation of resources to cover the increase in patients with respiratory infections and complications due to influenza for the duration of the epidemic, and, particularly in severe seasons, sharing experience between first-affected countries and those not yet experiencing peak influenza activity regarding optimization of the clinical treatment of patients. Influenza season's timing and spread metrics in combination with increasing body of evidence about influenza vaccine effectiveness by time since vaccination might contribute to more optimal timing of influenza vaccination campaigns in different European subregions. Furthermore, many changes are ongoing in the Region, including an optimization of influenza surveillance systems and changing population migration patterns, i.e. better connection between previously poorly connected areas and countries. These changes in combination with influenza virus's propensity to rapid changes itself indicate that continuous monitoring of influenza seasons' metrics are needed to influenza preparedness plans of upcoming seasons.

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Appendix 1. The list of countries/sub-national areas that, based on the inclusion criteria, reported virological (laboratory-confirmed influenza) and/or clinical (ILI and ARI) data.

Country	United Nations classification	Laboratory-confirmed influenza						ILI						ARI					
		08/ 09	**09/ 10**	**10/ 11**	**11/ 12**	**12/ 13**	**N of seasons**	**08/ 09**	**09/ 10**	**10/ 11**	**11/ 12**	**12/ 13**	**N of seasons**	**08/ 09**	**09/ 10**	**10/ 11**	**11/ 12**	**12/ 13**	**N of seasons**
Albania	Southern Europe	+	+	-	+	+	**4**	-	-	-	-	-	**0**	+	+	+	+	+	**5**
Armenia	Western Asia	-	+	+	+	+	**3**	-	-	-	-	-	**0**	-	+	+	+	+	**4**
Austria	Western Europe	+	+	+	+	+	**5**	+	+	+	+	+	**5**	-	-	-	-	-	**0**
Azerbaijan	Western Asia	+	+	+	-	+	**3**	-	-	+	+	+	**3**	-	-	-	-	-	**0**
Belarus	Eastern Europe	+	+	+	+	+	**5**	-	-	-	+	+	**2**	+	+	+	+	+	**5**
Belgium	Western Europe	+	+	+	+	+	**5**	+	+	+	+	+	**5**	+	+	+	+	+	**5**
Bosnia and Herzegovina	Southern Europe	-	+	+	+	+	**4**	-	-	-	-	+	**1**	-	-	-	-	+	**1**
Bulgaria	Eastern Europe	+	+	+	+	+	**5**	-	-	-	-	-	**0**	+	+	+	+	+	**5**
Croatia	Southern Europe	+	+	+	+	+	**5**	-	+	+	+	+	**4**	-	-	-	-	-	**0**
Czech republic	Eastern Europe	+	+	-	-	+	**3**	+	+	+	+	+	**5**	+	+	+	+	+	**5**
Denmark	Northern Europe	+	+	+	+	+	**5**	+	+	+	+	+	**5**	-	-	-	-	-	**0**
England	Northern Europe	+	+	+	+	+	**5**	+	+	+	+	+	**5**	+	+	+	+	+	**5**
Estonia	Northern Europe	+	+	+	+	+	**5**	+	+	+	+	+	**5**	-	+	+	+	+	**4**
Finland	Northern Europe	+	-	+	+	+	**4**	-	-	-	-	-	**0**	-	-	-	-	-	**0**
France	Western Europe	+	+	+	+	+	**5**	-	-	-	-	-	**0**	+	+	+	+	+	**5**
Georgia	Western Asia	-	+	+	+	+	**4**	-	+	+	+	+	**4**	-	-	-	-	-	**0**
Germany	Western Europe	+	+	+	+	+	**5**	-	-	-	-	-	**0**	+	+	+	+	+	**5**
Greece	Southern Europe	+	+	+	+	+	**5**	-	+	+	+	+	**4**	-	-	-	-	-	**0**
Hungary	Eastern Europe	+	+	+	+	+	**5**	+	+	+	+	+	**5**	-	-	-	-	-	**0**
Iceland	Northern Europe	-	-	-	+	+	**2**	-	-	+	+	+	**3**	-	-	-	-	-	**0**
Ireland	Northern Europe	+	+	+	+	+	**5**	+	+	+	+	+	**5**	-	-	-	-	-	**0**
Israel	Western Asia	+	+	-	+	+	**4**	+	+	+	+	+	**5**	-	-	-	-	-	**0**
Italy	Southern Europe	+	+	-	+	+	**4**	+	-	+	+	+	**4**	-	-	-	-	-	**0**
Kazakhstan	Central Asia	+	+	+	+	+	**5**	-	-	+	+	+	**3**	-	-	+	+	+	**3**
Kyrgyzstan	Central Asia	-	+	-	+	+	**3**	+	+	+	+	+	**5**	+	+	+	+	+	**5**
Latvia	Northern Europe	+	+	+	+	+	**5**	+	-	-	+	+	**3**	+	-	-	+	+	**3**
Lithuania	Northern Europe	+	+	+	+	+	**5**	+	+	+	+	+	**5**	+	+	+	+	+	**5**
Luxembourg	Western Europe	+	+	+	+	+	**5**	-	-	-	-	-	**0**	-	-	-	-	-	**0**
Malta	Southern Europe	+	-	-	+	+	**3**	-	-	-	-	-	**0**	-	-	-	-	-	**0**
Montenegro	Southern Europe	-	+	+	-	-	**2**	-	+	+	+	+	**4**	-	+	+	-	-	**2**
Netherlands	Western Europe	+	+	+	+	+	**5**	+	-	+	+	+	**4**	-	-	-	-	-	**0**

Northern Ireland	Northern Europe	+	+	+	+	+	**5**	+	+	+	+	+	**5**	-	+	+	+	+	**4**
Norway	Northern Europe	+	+	+	+	+	**5**	+	+	+	+	+	**5**	-	-	-	-	-	**0**
Poland	Eastern Europe	+	+	+	+	+	**5**	+	+	+	+	+	**5**	-	-	-	-	-	**0**
Portugal	Southern Europe	+	+	+	+	+	**5**	+	+	+	-	-	**3**	-	-	-	-	-	**0**
Republic of Moldova	Eastern Europe	-	+	+	+	+	**4**	-	+	+	-	-	**2**	+	+	+	+	+	**5**
Romania	Eastern Europe	+	+	+	+	+	**5**	-	+	+	+	+	**4**	+	+	+	+	+	**5**
The Russian Federation																			
Central	Eastern Europe	-	+	+	+	+	**3**	-	-	+	+	+	**3**	-	+	+	+	+	**4**
Far eastern	Eastern Europe	-	+	+	+	+	**4**	-	-	+	+	-	**2**	+	+	+	+	+	**5**
Northwestern	Eastern Europe	-	+	+	+	+	**4**	-	-	+	+	-	**2**	+	+	+	+	+	**5**
Siberian	Eastern Europe	-	+	+	+	+	**4**	-	-	+	+	+	**3**	+	+	+	+	+	**5**
Southern	Eastern Europe	-	+	+	+	+	**4**	-	-	+	-	+	**2**	+	+	+	+	+	**5**
Urals	Eastern Europe	-	+	+	+	+	**4**	-	-	+	+	-	**2**	+	+	+	+	+	**5**
Volga	Eastern Europe	-	+	+	+	+	**4**	-	-	+	-	+	**2**	+	+	+	+	+	**5**
Scotland	Northern Europe	+	+	+	+	+	**5**	+	+	+	+	+	**5**	-	-	+	+	+	**3**
Serbia	Southern Europe	+	+	+	+	+	**5**	+	+	+	+	+	**5**	-	-	-	-	-	**0**
Slovakia	Eastern Europe	+	+	+	+	+	**5**	+	+	+	+	+	**5**	+	+	+	+	+	**5**
Slovenia	Southern Europe	+	+	+	+	+	**5**	+	+	+	-	+	**4**	+	+	+	+	+	**5**
Spain	Southern Europe	+	+	+	+	+	**5**	+	+	+	+	+	**5**	-	-	-	-	-	**0**
Sweden	Northern Europe	-	+	+	+	+	**4**	+	+	+	+	+	**5**	-	-	-	-	-	**0**
Switzerland	Western Europe	+	+	+	+	+	**5**	+	+	+	+	+	**5**	-	-	-	-	-	**0**
Tajikistan	Central Asia	-	-	+	+	-	**2**	-	-	+	+	-	**2**	-	-	+	+	-	**2**
The former Yugoslav Republic of Macedonia	Southern Europe	-	+	+	+	-	**3**	-	-	-	-	+	**1**	-	-	-	-	-	**0**
Turkey	Western Asia	+	+	+	+	+	**5**	+	+	+	+	+	**5**	-	-	-	-	-	**0**
Ukraine	Eastern Europe	+	+	+	+	+	**5**	-	-	-	-	-	**0**	+	+	+	+	+	**5**
Uzbekistan	Central Asia	-	+	-	-	+	**2**	-	-	+	+	+	**3**	-	+	+	+	+	**4**
Wales	Northern Europe	-	-	-	-	+	**1**	+	-	-	+	-	**2**	-	-	-	-	-	**0**
Total number of countries/sub-national areas		**38**	**52**	**48**	**52**	**54**		**27**	**29**	**43**	**41**	**41**		**22**	**27**	**30**	**30**	**30**	