Surveillance of aseptic central nervous system infections in Poland: is it meeting its objectives?

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In Poland, a surveillance system capturing generic information on both diagnosed and undiagnosed aseptic central nervous system infections (ACI) has been in operation since 1966. This study evaluates to what extent the ACI surveillance is able to meet its objectives to monitor ACI trends and to detect signals of public health importance such as enteroviral outbreaks, tick-borne encephalitis (TBE) endemic foci, poliovirus appearance or emergence of new neurotropic viruses. Between 2004 and 2008, aetiology was established for 17% of ACI cases. Of the 1,994 reported ACI cases, 232 (11.6%) were diagnosed with TBE virus, 46 (2.3%) with enterovirus, 35 (1.8%) with herpesvirus, and 32 (1.6%) had other viral causes such as Epstein Barr virus or adenovirus. The system's performance varied between the provinces, with the frequency of suspected ACI cases referred for viral aetiology investigation in 2008 ranging from 1.98 to 285.4 samples per million inhabitants. The sensitivity of physicians' reporting, estimated as the proportion of hospitalised ACI cases reported to the surveillance system, was 48% nationally, with vast regional differences (range 30–91%). To conclude, the ACI surveillance system in Poland does currently not meet its objectives, due to limited availability of aetiological diagnosis and microbiological confirmation and to regional differences in reporting sensitivity.

Background

Viruses are a common cause of central nervous system (CNS) infections in humans. There is increasing evidence that new neurotropic viruses, mostly of zoonotic origin, emerge regularly [1-5]. Many of these viruses can lead to outbreaks, thus increasing their public health importance [3,4,6,7]. Concrete data on the burden of different neurotropic infections are however limited [8].

In relation to neuroinvasive pathogens, all countries should have efficiently operating surveillance systems for aseptic central nervous system infections (ACI) in place that are able to identify potential threats and raise timely alarms, especially if international spread is involved. *Enterovirus* surveillance systems implemented in several countries have proved to be efficient alternatives to the acute flaccid surveillance and play an important role in the Global Polio Eradication Initiative [8,9].

In Poland, a surveillance system aimed at the collection of generic information for all diagnosed and undiagnosed ACI cases was implemented in 1966. There is no official document in which operational objectives of the system are defined. For the purposes of this paper, we summarise the objectives of the system as follows, taking into consideration current national public health priorities: (i) monitoring overall ACI trends in order to detect outbreaks caused by neurotropic viruses (most commonly coxsackieviruses and echoviruses belonging to the *Enterovirus* family); (ii) identification and monitoring of tick-borne encephalitis (TBE) endemic areas in order to develop evidence-based TBE vaccination recommendations; (iii) monitoring *Enterovirus* strains and referring them for identification of polioviruses as part of the Global Polio Eradication Initiative; (iv) detection of signals indicating the possibility of emergence of neurotropic viruses not yet seen in Poland.

To achieve these objectives efficiently, the ideal surveillance system should perform well at both national and sub-national level, sensitively detect potential public health threats, and ensure regional availability of neuroinvasive virus diagnostics to enable timely and efficient interventions in situations such as enteroviral outbreaks, newly identified TBE foci or poliovirus spread.

The aim of the present study was to evaluate the ACI surveillance system in Poland according to selected performance indicators, with special focus on regional differences in its performance.

Material and methods

The Polish ACI surveillance system is based on notifications from physicians. Physicians are required by law to notify suspected cases, i.e. those with signs of aseptic meningitis, encephalitis and/or myelitis, to the district sanitary-epidemiological stations (SES). Diagnosed ACI cases for which the viral aetiological agent has been identified, as well as cases classified as ACI of unknown aetiology or viral, unspecified ACI are reported to surveillance. Reports on incident ACI cases are aggregated and forwarded every two weeks to the provincial SES, where, in turn, they are aggregated and sent to the Department of Epidemiology at the National Institute of Public Health (PZH). Currently, each case is assigned to one of nine reporting categories based on the WHO International Classification of Diseases (ICD) (Table 1). Standardised case definitions are used for reporting of TBE and West Nile virus (WNV) infections. In case of TBE, a local case definition was developed [10], and for WNV the EU 2008 case definition was adopted [11].

In each of the 16 Polish provinces, laboratories in the public and private sector offer diagnostics for the most common ACI aetiological agents. Currently, the majority of laboratories receive payment for performing these tests, which are covered by the referring organisation. Only in some public health laboratories is testing of stool and cerebrospinal fluid for enteroviruses performed free of charge.

In the present paper we have summarised data on reported ACI cases, based on annual surveillance reports from 2004 to 2008 [12].To assess the availability of diagnostic testing for viral ACI aetiology we used the results from a survey on the availability of diagnostics for CNS infections conducted in the period from March to December 2009 and covering all Polish provinces. The respondents were 318 epidemiologists working in district SES. Each epidemiologist provided information from hospitals under their responsibility. From each hospital, information on the possibility to hospitalise ACI cases was requested, as well as on the availability of laboratory diagnostics for viral pathogens in the hospital or a subcontracted laboratory. We supplemented the above survey with information on the number of samples tested for viral pathogens in 2008, obtained from an ad hoc survey of laboratories that were identified as offering ACI viral diagnostics in the main survey. We estimated the number of cases referred for diagnosis of ACI viral pathogens in each province. Because of the increasing role of magnetic resonance imaging (MRI) in the diagnosis of herpes simplex encephalitis based on characteristic cerebral lesions [13], we also assessed the availability of MRI in Polish hospitals in the national hospitals registry [14]. All the above information on the availability of ACI diagnostics was collected for the year 2008. We assessed the differences between the 16 provinces by computing measures of location and dispersion (sum, mean, standard deviation, range, median and interquartile range). We compared the frequency of referral for diagnosis of viral aetiology with ACI incidence in each province through scatter plots and computation of Spearman correlation coefficients.

To assess the sensitivity of ACI surveillance during the studied period 2004 to 2008, we compared aggregated data on ACI cases reported as part of routine surveillance with hospital discharge data that are collected annually from approximately 90% of Polish hospitals by the Department-Centre of Monitoring and Analyses of Population Health at PZH. In both systems ICD-10 codes are used to classify diagnosed diseases and syndromes, and for the present assessment we used five-digit codes used in the surveillance system (Table 1). Primary and up to five secondary causes

Table 1

List of diseases and syndromes reported in the Polish surveillance system for aseptic central nervous system infections

ACI syndrome	ICD-9 codes (1972-1996)	ICD-10 codes (1997-2008)
Viral encephalitis: tick-borne	063	A84
West Nile fever	-	A92.3
Viral encephalitis: herpesvirus	054.3	B00.4
Viral encephalitis: other virus, specified	062; 064; 323.1	A81.1; A83; A85; B02.0
Viral encephalitis: unspecified	049.9	A86
Encephalitis: other and unspecified	323.8; 323.9	G04.8-9
Viral meningitis: enterovirus	047	A87.0
Viral meningitis: herpesvirus	054.7	B00.3
Viral meningitis: other specified and unspecified	049.0; 049.1; 053.0	A87.1-9; B02.1
Meningitis: other and unspecified	322	G03

ACI: aseptic central nervous system infection.

of hospitalisation included in the discharge records were extracted from the database and assigned to the patient's province of residence. To account for the diverse proportion of hospitals reporting monthly in particular Polish provinces, we weighted the annual number of hospitalised cases by province, with an underreporting factor constructed in the following way:

$$weight_{(province,year)} = \frac{\sum_{H_{(prov,year)}} B*12}{\sum_{H_{(prov,year)}} B*M}$$

where B is the number of hospital beds, M the number of reporting months summed for hospitals in a given province in a given year, and H all registered hospitals in a given province in a given year.

We evaluated the sensitivity of statutory notifications by calculating the proportion of hospitalised cases that were reported to surveillance. We computed 95% confidence intervals (CI) of obtained sensitivity estimates using the formula for binomial proportions. For data analysis we used STATA version 10 [15].

Results

Incidence of aseptic central nervous system infections

In the period 2004 to 2008, aetiology was established for 17% of reported ACI cases in Poland. From the annual average of 1,951 ACI cases reported, 238 (12.2%) were diagnosed as TBE, 46 (2.4%) as enteroviral, 35 (1.8%) as herpes simplex ACI, and 32 (1.6%) as another viral cause such as Epstein Barr virus, adenovirus or other. It was presumed that the viral aetiology of an ACI with unknown cause was based on the general examination of cerebrospinal fluid, and MRI results.

The reported incidence of ACI differed considerably between Polish provinces in the period 2004 to 2008 (Figure 1). An almost 10-fold difference was seen between provinces, with the lowest recorded in Lubuskie and the highest in Podlaskie (20.2 versus 191.4 per million inhabitants, $p<10^{-4}$). This difference could be partly explained by the high TBE incidence in Podlaskie province, however after omitting confirmed TBE cases, the difference in incidence between the two provinces was still almost five-fold (20.2 versus 96.9 per million inhabitants, $p<10^{-4}$).

Availability of diagnostics for aseptic central nervous system infections in hospitals

According to the survey on the availability of ACI diagnostics, 185 of the 863 hospitals functioning in Poland in 2008 admitted ACI cases (301 wards). ACI cases were admitted predominantly to infectious disease and neurologic units, with occasional admissions to paediatric, internal medicine or intensive care units. Regional differences in the availability of ACI diagnostics were observed. The frequency of suspected ACI cases referred for viral aetiology investigation ranged from 1.98 to 285.4 samples per million inhabitants in the different provinces. Table 2 summarises the descriptive statistics for regional differences in diagnostic performance for ACI.

Serological diagnosis of TBE was available in four laboratories in Poland, which offered ELISA testing for IgM and IgG antibodies against TBE virus. During 2008, these laboratories processed serum or cerebrospinal fluid samples from 908 patients, of which 211 were found positive. Most of the tests were requested for suspected ACI cases living in high-risk areas for TBE, with 60.1% samples referred from three provinces where TBE incidence exceeded 5 per million inhabitants, and 91% samples referred from seven provinces where the TBE incidence was over 1 per million inhabitants (Figure 1). For enteroviral infections, serological diagnosis and isolation from stool samples were available in the 16 public health laboratories located in province capitals; PCR testing for these viruses was not available in Poland during the survey period. Of 568 samples referred for detection of antibodies against

Table 2

Selected indicators of the performance of diagnostics for aseptic central nervous system infections, Poland, 2004–2008

		Sum	Mean	SD	Range	Median	IQR
Units hospitalising ACI	Total	301	19	16	5–71	13	11–22
	Per million inhabitants	-	7.5	3.3	3.5–5.2	6.3	5.0–9.6
Samples tested for TBE	Total	908	57	86	0–241	16	5–57
	Per million inhabitants	-	34.6	61.4	0–202.3	5.5	1.5–39.3
Samples tested for enteroviruses	Total	568	36	37	0–118	26	10–53
	Per million inhabitants	-	16.9	17.5	0–52.3	11.7	3.6–25.5
Samples tested for other viruses	Total	718[a]	45	46	2–141	27	10–66
	Per million inhabitants	-	20.1	22.9	2.0–82.3	10.9	4.6–27.9

ACI: aseptic central nervous system infection; IQR: interquartile range; SD: standard deviation; TBE: tick-borne encephalitis.

[a] of which seven were tested for herpes simplex virus as well as for other viruses, adding up to 725 tests.

enteroviruses in 2008, 57 were determined as positive. For confirmation of herpesviral CNS infections, MRI testing was available in 100 hospitals throughout the country, and PCR diagnosis, currently the reference diagnostic method to confirm herpes simplex virus infection, was offered by four laboratories (both paid for by the referring hospitals). According to our survey, 568 patients were tested for antibodies against herpes simplex virus, and 113 were found positive. Other aetiological agents of viral ACI, including adenovirus, Epstein-Barr virus, cytomegalovirus, mumps, varicella-zoster or measles viruses were investigated in 157 cases, of which 45 were found positive.

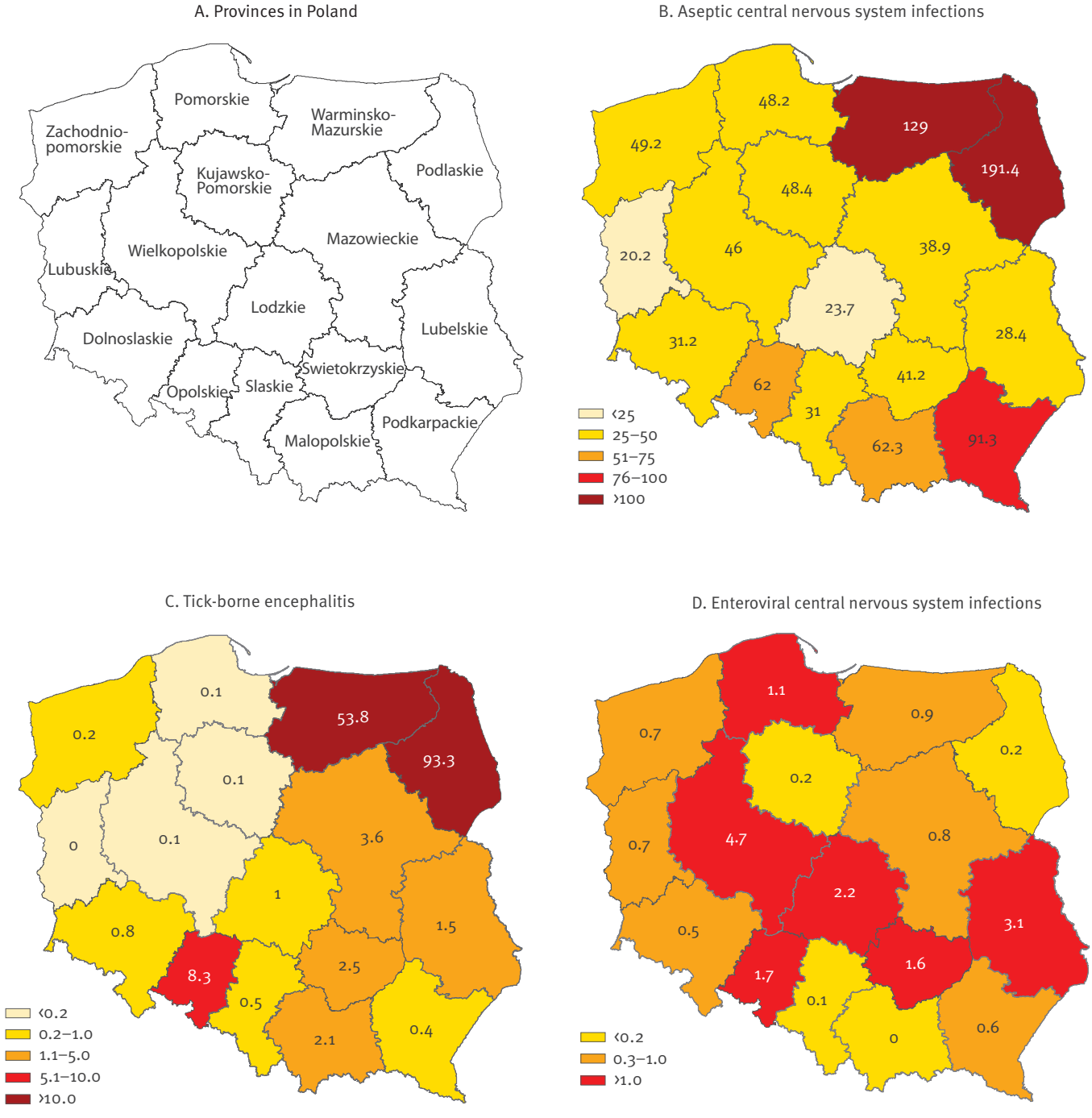
Sensitivity of reporting of aseptic central nervous system infections

The assessment of ACI reporting sensitivity is summarised in Table 3. From a total of 20,377 ACI cases recorded in Polish hospitals between 2004 and 2008, 9,754 (47.9%) cases were reported to the national surveillance. Important differences in the surveillance sensitivity were observed by year, reporting syndrome, and province.

When the province-specific frequency of referral for viral aetiology diagnosis was compared with ACI incidence, we noted a statistically significant moderate

Figure 1

Average incidences of aseptic central nervous system infections per 1,000,000 inhabitants by province, Poland, 2004–2008



correlation with the incidence of reported ACI (r_s=0.62, p=0.011) but no correlation with the incidence of hospitalised ACI (r_s=0.43, p=0.0097). Plotting the regional frequency of referral for viral testing against the ACI incidence revealed that the same three provinces with known TBE endemic foci were clear outliers, both for hospitalised and reported ACI cases (Figure 2).

Figure 2. Frequency of referral for diagnosis of the viral aetiology of aseptic central nervous system infections in 16 provinces, Poland, 2004–2008

Discussion

In the present study we analysed the performance of the ACI surveillance system in Poland according to selected indicators. Combining data from different sources, we observed important regional differences in the system's performance. Aetiological diagnosis, a key factor in three of the four surveillance aims, was not uniformly available in all Polish provinces. Moreover, regional differences were observed in the physicians' approach towards reporting of ACI cases with specified or unspecified viral cause.

Table 3

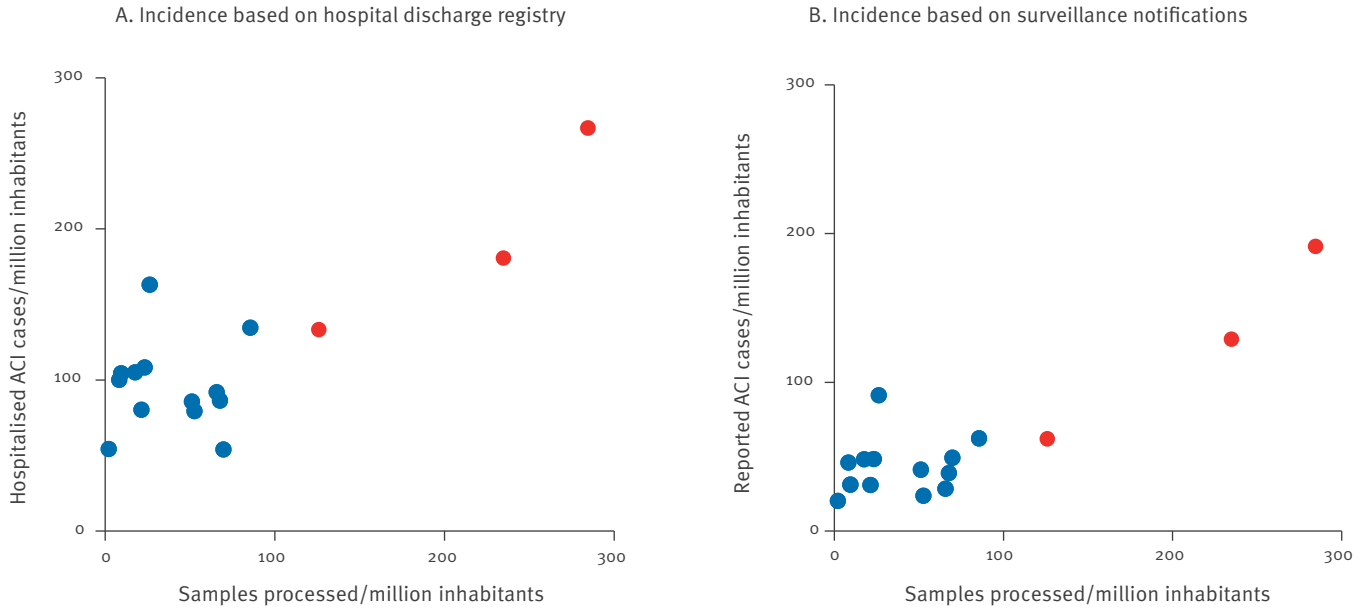
Sensitivity of surveillance for aseptic central nervous system infections by reported syndrome, disease severity and province, Poland, 2004–2008 (n=20,377 hospitalised cases)

	Hospitalised cases	Reported cases	Proportion reported	95% CI
Reported syndrome				
Viral ACI, specified	2,496	1,354	54.2	52.23–56.17
Viral ACI, unspecified	9,055	6,258	69.1	68.12–70.03
ACI other, unspecified	8,826	2,142	24.3	23.37–25.17
Reported disease severity				
Meningitis	16,190	6,894	42.6	41.82–43.35
Encephalitis	4,187	2,860	68.3	66.87–69.71
Province				
with lowest sensitivity	1,019	304	29.8	27.04–32.75
with highest sensitivity	457	417	91.2	88.27–93.67

ACI: aseptic central nervous system infection; CI: confidence interval.

Figure 2

Frequency of referral for diagnosis of the viral aetiology of aseptic central nervous system infections in 16 provinces, Poland, 2004–2008



ACI: aseptic central nervous system infection.
Red dots indicate provinces with tick-borne encephalitis incidence exceeding five cases per million inhabitants during 2004–2008.

Poor availability of aetiological diagnosis in Polish hospitals is an important limitation of the ACI surveillance system. Most Polish provinces are not able to reach any of the four stated surveillance objectives. Firstly, the public health system is probably not detecting the majority of enteroviral outbreaks, as only sporadic cases are diagnosed with enterovirus aetiology and the potential outbreak cases can remain undetected in the mass of undiagnosed cases. Secondly, the ACI surveillance system could be an efficient tool for detecting the location of TBE foci and monitoring its changes, if unspecified ACI cases were referred for testing in all provinces. In provinces not known for high TBE incidence, most locally acquired and imported TBE cases are not diagnosed and remain recorded in the surveillance system as ACI cases of unknown aetiology. Thirdly, it is highly unlikely that cases of polio would be differentiated from cases of aseptic meningitis, particularly if poliovirus is imported from endemic areas in Africa or Asia. Meningitis cases are rarely referred for enterovirus detection, and only as few as two strains and 18 samples for poliovirus isolation from ACI cases throughout the country were sent in 2008 to the National Polio Laboratory at the PZH (personal communication, Magdalena Wieczorek, July 2011). Finally, there is very little chance to detect the emergence of yet unknown viruses causing aseptic meningitis or encephalitis, because suspected ACI cases are rarely tested for viral aetiology. Valid monitoring of neurotropic viruses would require application of standard diagnostic protocols in Polish hospitals, and the possibility of cost-free referral of at least 10% of undiagnosed samples to regional or national reference laboratories.

We can hypothesise that Polish physicians may consider it an unnecessary cost to investigate the viral aetiology since no aetiological treatment is available for most viral ACI except herpes simplex CNS infections. Currently, the National Health Fund, which covers hospitalisation costs, offers the same refund for hospitalisation of ACI cases irrespective of whether the aetiology is confirmed or not. Sparse evidence from European studies indicates that diagnosis of viral pathogens as a cause of CNS infections is also rarely performed in other European countries [8,16].

The regional differences in surveillance sensitivity across Polish provinces (mean 48%, range 30-91%) may be related to different levels of activity of local public health offices, and willingness of physicians to collaborate with the public health system. According to crude data, the highest reported ACI incidence, and some of the highest estimates of surveillance sensitivity were seen in provinces in which TBE diagnostics were widely available (data not shown). Sensitivity of reporting was lower for cases with milder symptoms (meningitis without signs of brain involvement), and for cases classified as 'other' and 'unspecified ACI', comprising all cases which could not be determined as either viral or bacterial.

Although national surveillance systems are the responsibility of the national authorities, there is increasing recognition of the need to collect supranational disease estimates and estimate the international disease burden, to better plan public health resources and detect public health threats. Because increasing international traffic facilitates the spread of infectious diseases, public health research should focus more on the setup and performance of national public health surveillance systems in order to better understand the meaning of numbers provided by the countries. If for example a new food- or waterborne viral strain appeared in a European setting, causing, among others, symptoms of meningitis, one would want to be sure of its timely detection, using standardised laboratory methods, in each country in which it appeared, before it spreads so far as to prevent efficient interventions.

The estimates presented here have several limitations. For the survey of ACI diagnostic availability, the SES did not approach hospitals that had not reported cases in a number of years, assuming that these did not hospitalise ACI cases but referred them elsewhere. Because not all hospitals comply with the procedures of reporting to the local SES, this could have led to underestimation of ACI-hospitalising units. The ad hoc survey of ACI diagnostic testing performance was limited to the major diagnostic laboratories. We could therefore have missed samples referred for testing to other laboratories, for example in the private sector. Since the number of positive samples estimated by our survey matched closely the number of reported cases with established aetiology, we think that our estimates correctly reflect the diagnosis of ACI cases of probable viral aetiology in Poland. Also, the estimation of the physicians' notification sensitivity may be biased, as we compared two different data sources. The weighting factor did not take into account the type of unit in reporting hospitals. If hospitals that were not reporting discharge codes had fewer infectious disease or neurological departments than reporting hospitals, the weighted number of recorded ACI cases could have been overestimated. On the other hand, the majority of units that do not report to the hospital registry are university hospitals which have a higher frequency of admitted ACI cases compared to general hospitals. This would therefore lead to an underascertainment of hospitalised ACI cases.

To conclude, the Polish ACI surveillance system is not meeting most of its objectives, mainly because ACI aetiological diagnosis is not readily available to hospital physicians and because physicians' reporting is inconsistent. More research is necessary to understand the reasons for the poor compliance of physicians with mandatory reporting and for the regional differences in the performance of ACI surveillance. Furthermore, complete evaluation of the ACI surveillance system would be beneficial, using the criteria listed in the guidelines published by the United States Centers for Disease Control and Prevention [17]. Like

other communicable disease surveillance systems in Poland, the ACI surveillance was implemented several decades ago, at a time when highly centralised surveillance systems were operating uniformly in all countries of the Warsaw Pact. Similar to other systems, ACI surveillance has never been evaluated, nor have its goals been stated. Polish society has gone through important changes during the past three decades and it is therefore important to understand whether the communicable disease surveillance objectives defined for the system more than 40 years ago are still valid.

Recommendations

Based on the results of the present evaluation we recommend the following:

1. Allocation of resources to improved diagnosis of ACI through, i.e. offering diagnosis for selected neurotropic viruses of public health importance in public health laboratories free of charge, or at least at reduced price;
2. Implementation of uniform diagnostic protocols in hospitals, including differential diagnosis of most common causes for ACI and their virological investigation;
3. Creation of a network of hospitals, from which cases would be referred for extended epidemiological and virological investigation of ACI cases in reference laboratories.

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