Quantification of qualitative influenza indicators used in EuroFlu and TESSy

TECHNICAL REPORT ON
AGREEMENT FOR PERFORMANCE WORK
- WHO Collaborative Activities-

WHO Registration no. 2012/227590-0

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22nd November 2012

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1 Executive summary

The WHO Regional Office for Europe (WHO/Europe) and ECDC jointly coordinate the European surveillance network for influenza, which collects weekly data on quantitative and qualitative indicators for influenza from more than 50 Member States. A recent evaluation of the use of the qualitative indicators (geographical spread, intensity, trend, impact and dominant virus) showed that there were considerable differences in the interpretation of the definitions and that discrepancies between weekly reported qualitative and quantitative data frequently occurred.

In the Annual Meeting in Ljubljana, in June 2011, most of the participants acknowledged that reporting on the indicators was prone to error and suggested that WHO/Europe and ECDC establish a working group to assess the feasibility and value of quantifying the current qualitative indicators. It was also proposed that automated calculations of the indicators 'trend' and 'intensity' should be explored, including integrating virological data in the calculations, if feasible, to increase the robustness and accuracy of the indicators.

A working group (WG) started to review this issue in February 2012 and after two WG meetings (one of them by teleconference) and two Annual Meetings with all EU/EEC and with the New Independent States, in June 2012 and September 2012 respectively, a great number of ideas, problems, solutions, conclusions and recommendations were proposed to be implemented in the coming seasons.

A review of the current situation and the possibilities to improve the validity of the QI was done in the framework of an Agreement for Performance of Work signed by the WHO Regional Office for Europe and the Foundation of the Institute of Health Sciences Studies of Castilla y León (Spain). Also different quantitative approaches were tested with historical data from 20 countries.

The outcomes of all this work is a list of conclusions and recommendations which could be summarised in:

The current situation of QI in flu surveillance presents still some problems of validity and comparability, despite the interest and usefulness showed by the European countries.

Intensity, Trend and Dominant Virus are the three QI prioritised to be defined and standardized trough a more objective methods (quantitative, algorithms, etc.)
It is necessary to pilot these methods in a significant number of volunteer countries and to assess their performance and validity.

2 Terms of reference (TOR)

2.1 Aim of the agreement

Investigate methods to quantify the qualitative influenza indicators below in order to present robust and comparable data.

a) Intensity.
b) Geographic spread.
c) Trend.
d) Impact.
e) Dominant virus type.

2.2 Specific tasks under the Agreement of Performance of Work

I. Inventory of existing methods to quantify influenza indicators:
   a. To carry out an email survey to Member States to investigate if countries have established methods to quantify qualitative indicator
   b. To collect information on the method used by Member States (e.g. national intensity thresholds)
   c. To summarize the results and to assess robustness of national methods.

II. To define for each of the indicators other possible methods to quantify or semi-quantify the qualitative indicators and assess quality and robustness. Investigate if the Moving Epidemic Method (MEM)[1] can be used to define intensity levels and assess the results for different confidence limits.

III. To summarize the results and advantages and disadvantages of the different methods and develop a proposal on the preferred method for each of the four indicators. Prepare a draft plan to be presented to the EISN Coordination group.

IV. To present a proposal of the methods to the Qualitative Working Group at the expert meeting.

V. To summarize the output of the Working Group Meeting and include feedback in the Proposal to be presented at:
   a. The ECDC/WHO EURO Joint Annual Influenza Surveillance Meeting for Western, central and south eastern European countries (May 29th-June 1st, 2012)
   b. The Annual WHO Influenza Surveillance Meeting for New Independent States (WHO) (11-14 Sep 2012).

VI. To provide a short report and data and/or information to assure pilot testing of the proposed method in the 2012- 2013 season in selected countries in Europe.

3 Introduction

3.1 Background

The use of qualitative indicators (QI) in influenza surveillance in Europe started in the season 2000-2001, when the weekly reports of the former EISS (European Influenza Surveillance Scheme) introduced the dominant virus type and the geographical spread. Later, in 2002-2003 the intensity indicator was displayed on the website and the different baseline methods were discussed in order to standardize country information on influenza activity. In the season 2003-2004 some countries begin to introduce their own baseline in the website. These first definitions and criteria were assumed by WHO[2] and ECDC[3] and are still in use in the current international reports.

The working group that have been studying the performance of the QI for the EISS continues its works in the framework of the joint WHO Europe and ECDC European Influenza meetings, discussing the current use in flu surveillance, the usefulness and the improvement margin.

An evaluation of the performance of the four qualitative indicators (geographical spread, intensity, trend and impact), which are used to classify levels of influenza transmission according to standard definitions, was performed in May 2011 coordinated jointly by WHO/Europe and ECDC.

The evaluation showed that:

1. The majority of countries (>90%) reported geographical spread, intensity and trend with a high level of reporting completeness throughout the season.
2. Impact was only reported by about half of the Member States with relatively low reporting completeness.
3. There were substantial differences in the interpretation of the indicators among countries.
4. Discrepancies between weekly reported qualitative and quantitative data were often observed.

The evaluation was presented and discussed at the Joint ECDC/WHO Regional Office for Europe Meeting on Influenza Surveillance in Ljubljana Slovenia, 7-9 June 2011[4]. As results of this discussion, it was proposed to establish a working group to assess the feasibility and value of quantifying the current qualitative indicators.

This could be done by *automated calculations* for the indicators 'trend' and 'intensity', and should (if feasible) *include the integration of virological data* in the calculations to increase the robustness of the indicators.

3.2 Rationale

Influenza surveillance is based on different sources information:

a) Estimated rates of ILI outpatient consultation (sentinel sites or nationwide systems).
b) Virological surveillance.
c) Mortality surveillance
d) Hospitalisation surveillance (including intensive care admissions)
e) Other: outbreaks, sick leaves, scholarship absenteeism etc.

Not all sources are available in all countries across Europe and the quality of the information varies in terms of accuracy, validity and opportunity.

This information is used by the surveillance systems to assess the influenza activity, either monitoring the situation weekly or using a global measure over the whole season, through the INDICATORS OF INFLUENZA ACTIVITY.

Quantitative indicators of influenza activity:

a) ILI/ARI consultation incidence rate (population based or consultation based)
b) Influenza specific mortality rate (or ILI/Pneumonia or total mortality rate)
c) Percentage of lab positives test (culture/molecular) in swabs taken in ILI patients.

Qualitative indicators of influenza activity:

a) Intensity
b) Trend
c) Geographical spread
d) Dominant virus type
e) Impact

Although the first ones need still an effort of standardisations and the improvement of the quality of data sources[5] [6][7], they are quite well defined. However, the last ones lack of clarity, they are not easy to collect and they are subject to local and subjective interpretations that difficult the comparability among countries and restrict the usefulness.

The origin of the qualitative indicators in use in Europe, are the US indicators which have been used by the Epidemiology and Prevention Branch in the Influenza Division at CDC the CDC, especially in geographical spread and the map overview of the influenza activity.

The difficulties to objectively assess the extent of an epidemic are clearly stated in this document: 'the state and territorial epidemiologists' reports of the geographic spread of influenza activity and the ILI activity indicator display state-level information'[8]

4 Methodology

4.1 Review of the quality indicators for influenza surveillance. Definition, methods, feasibility and usefulness.

In this first phase we explore in the scientific documents the acceptability and simplicity, sensitivity and specificity, representativeness, timeliness, resources and communication of the QI

Timeliness is a very important characteristic of the indicators because of the relevance when control measures must be taken. Timeliness of the indicators is limited by the availability of the data and the cost (human and technological resources) of delivering the information timely (weekly). However, not all the indicators in influenza surveillance must be necessarily calculated in a weekly basis. Some of them could be calculated at the end of the seasonal period to make descriptive or analytical studies to best understand the epidemiology of the ILI/ARI epidemics.

4.1.1 Intensity

Aim: Comparison among countries or regions (place), historical series data (time) and populations (persons).

Definition: Quantification of the maximum level reached by the indicator (incidence rate, nr of consultations etc.)

Options: The four levels in use (low, medium, high and very high) can be defined through:

- Incidence rate (population based indicator)
- Consultation proportion (consultation based indicator)

A different number of levels could be established, but these 4 are well known in Europe and easily to understand and assimilate for most of the countries.

Any mathematical model working with time series data which allow to estimate the 'average' level reached by the epidemics in a specific place (country, region ..).

- The MEM method makes these calculations with the epidemic periods and produces statistical intervals to define intensity levels.
- The PERCENTILE method estimates percentiles based in all avalaible data.

A minimum of 5 seasons are necessary for this calculus.

Secular trend of influenza epidemics should be taken in count to model this 'average' level.

Age standardisation must be bear in mind when:

- Rates are estimated from sentinel (sample) surveillance systems in which some age groups could be overrepresented (e.g. SN with paediatricians)
- Comparisons between populations with different age structure.
- Large time series analysis.

Intensity levels calculated by MEM show a homogeneous distribution of seasons' intensity although there is a small bias towards low levels because MEM only uses epidemic periods. MEM provides intervals based in confidence. Intensity levels calculated by PERCENTILE methods show a distribution of seasons' intensity biased toward high levels, because the thresholds are located in the low rates.

Source of data: Primary care consultations for ILI or ARI and list of patients by age group in population based rate.

Periodicity: Weekly basis.
Daily basis would be possible where computerised systems (Electronic Medical Record) are available. There is no evidence that a periodicity shorter than a week improve the quality and the usefulness of the ILI/ARI surveillance, whereas the cost is extremely high.
A whole **seasonal estimate of the incidence** (when the seasonal surveillance is over) is necessary to detect high seasonal rate with moderate weekly intensity levels in epidemics with long duration or bimodal waves.

Usefulness: Intensity is a relevant indicator in ILI/ARI surveillance. This indicator serves to:

- Compare different seasons in the same place or different populations (age group, vaccinated vs. no vaccinated …) in the same place.
- Compare different places where the surveillance systems are comparable (in the same country, similar sentinel systems etc.)
- Allow the comparison of rates between different countries is difficult and imprudent because the different source of data, population structure, economical, social and work peculiarities. But, intensity levels established by the same method in different countries, represents the same value, which can be perfectly comparables.

4.1.2 Trend

Aim: Determine if the (current situation of the) epidemic is ascending, constant or descending. .

Definition: General course that follow the incidence rate of ILI/ARI at a specific moment.

Options:

- Simple comparison between two weekly rates: Increasing, unchanged, decreasing.
- Number of consecutive tendency in weekly rates comparison (two?) to define a general course of the influenza activity.
- |rate n – rate n-1| /rate n-1 >10-20% increasing or decreasing; <10-20% unchanged.
- Statistical comparison (statistical significant differences between two weekly rates): Increasing and decreasing with SSD . Unchanged: No SSD.

Source of data: Primary care consultations for ILI or ARI and list of patients by age group in population based rate..

Periodicity: If two consecutive weeks are necessary for the general course, two weeks of delay in the critical periods (pre-epidemic to epidemic, at the peak and the end of the epidemic period)

Usefulness: Great interest for public health officials (policy makers) and health services providers.

4.1.3 Geographical spread (Diffusion)

Aim: Provide evidences that the epidemic is affecting a large area (several regions/countries). To know how the disease is expanding over a large geographical area.

Definition: The degree of the extent of the disease at the moment in the frame of a geographical area.

Options:

- Geostatistics (Kriging): used in Spain and other countries to interpolate rates from rates calculated in a sample of points. Kriging is a quite sophisticated mathematical method which needs accurate rates in a well geographical dispersion sample of points. Large sample errors on the interpolation estimates, particularly in the borders of the country. Time and computer resources consuming. Difficult to issue in a weekly basis.
- Automated algorithm with the WHO/EISN based in two type of data: weekly rates (a baseline or threshold is needed) and virological data (not always precise and timeliness at the beginning of the epidemic period).
- A simple calculation based in the percentage of notification could be an alternative: The variables necessaries are week, area, notification points with cases and without cases. The indicator would be the % of points with cases in a week.

A simple algorithm with a minimum of five variables (week, area, threshold, weekly rate and number of virus detection) would be implemented in the European surveillance platforms.
Limits: not all surveillance systems know the number of notification points at national level to be transmitted.

Source of data: This information must be available at the local/regional/country level and these geographical areas should be defined.

Periodicity: Weekly calculations could be possible.

Usefulness: Geographical spread has been one of the most studied indicators in infectious diseases. Its relevance is out of any doubt for most of the communicable diseases. Space distribution of the disease is necessary to understand the natural course of the disease and epidemics, and for taking the appropriate control measures. In the specific case of the influenza, the assessing of geographic spread could be no so relevant because the sudden onset of the epidemic, the quick diffusion through regional/country borders and the shortness of the epidemic period (in one or two

weeks the incidence rate is doubled or tripled and in 4-6 weeks the peak is usually reached).

4.1.4 Dominant virus type

Aim: To determine if the distribution of circulating viruses by region/country is homogeneous or one or more viruses are predominant.

Definition: A prevailing tendency of one virus type (or subtype) over other.

Options:

- Simple percentage of types/subtypes out of (denominator) all swabs or positives swabs or positives type A. Confidence limits should be calculated to avoid random errors and to ascertain the predominance of one strain over other or co-dominance (independently of the percentage)
- Odds of one type/subtype over other. Type A/type B; H1/H3 (not total number of swabs or negatives is necessary)

Source of data: Data are commonly available (completeness checking of all lab results must be assured)

Periodicity: Weekly (dominant virus for the single current week) and Cummulated (a global dominant virus for the whole season, from the beginning to the current week).

Usefulness: Different dominant virus type in nearby regions/countries could indicate risk of spread in a naive population. The study (wide research) of different virus distribution will help to understand the onset of influenza epidemics.

4.1.5 Impact

Aim: Assess the effects of the epidemics in the health, social and economical aspect in the population.

Definition: the significance or major effect of the influenza epidemics in the population.

Options: Influenza epidemics (and especially influenza pandemics) have an impact on health (morbidity and mortality), social and economics (works/scholar days lost, transports, social alarm, health cost) and in general disrupt the normal life of a community.

- *Hospitalisation surveillance*: In the US, FluSurNet. Same protocol in 16 urban and suburban sites. Case definition: hospitalized and influenza test positive. Submit data every 2 weeks via FTP site –moving to web-based. 8% of US Population.
- *Visits to the Hospital Emergency Department*: In selected hospitals in CyL, total and paediatric. Weekly basis. Computerised scheme. Indicator: excess of visits (adults/children).
- *Mortality surveillance:* robust information and robust indicators. Good mathematical models and time series analysis to assess the excess of mortality. Limitations: poor (or problems with) timeliness (in US reporting lag 1-2 weeks); unspecific monitoring, causes of dead not always codified and variations in the selection (influenza, influenza plus pneumonia, others)
- *Intensive Care Unit surveillance:* Establish during the 2009-2010 pandemic in some developed countries. No longer in operation in most of them.

Source of data: different sources depending of the indicator.

Periodicity: weekly if possible.

Usefulness: Measure of the severity.

4.2 Working group

A working group was constituted with the aim of evaluate the necessities, the usefulness and the methods to quantify the qualitative indicators on flu surveillance.

The specific objectives of the working group are to:

- Review the definitions for the qualitative indicators: Geographical spread, intensity, trend, impact and dominant virus; and their use in influenza surveillance;
- Discuss a proposal for quantifying selected qualitative indicators, including automated calculations of these on the EuroFlu/TESSy platforms;
- Provide recommendations on the need for revision (including modification of current definitions, quantification, or semi-quantification) for each of the five indicators.

Expert from some European countries and representatives from WHO Headquarters, WHO Europe and ECDC were invited to join this group.

Members of the WG

Member states experts
Dr Jan Kyncl (Czech Republic)
Dr Silke Buda (Germany)
Dr Siri Helene Hauge (Norway)
Dr Dragana Dimitrijevic (Serbia)
Dr Alla Miranenko (Ukraine)
Dr Richard Pebody (United Kingdom)

WHO Influenza Centre, United Kingdom
Dr Rod Daniels

ECDC
Prof. Angus Nicoll

WHO Regional Office for Europe
Dr Caroline Sarah Brown
Ms Pernille Jorgensen
Dr Ganna Bolokhovets
Dr Dmitriy Pereyaslov
Dr Tamara Meerhoff (consultant)
Dr A. Tomás Vega Alonso (consultant)

WHO Headquarter
Dr Terry Gail Besselaar
Dr Julia Fitzner
Dr Kaat Vandemaele
Dr Tony Mount

4.3 Survey on influenza quality indicators

The objective of the survey (Appendix 1) was to collect information on the definition used and existing methods to quantify influenza indicators *(e.g. national intensity thresholds)*

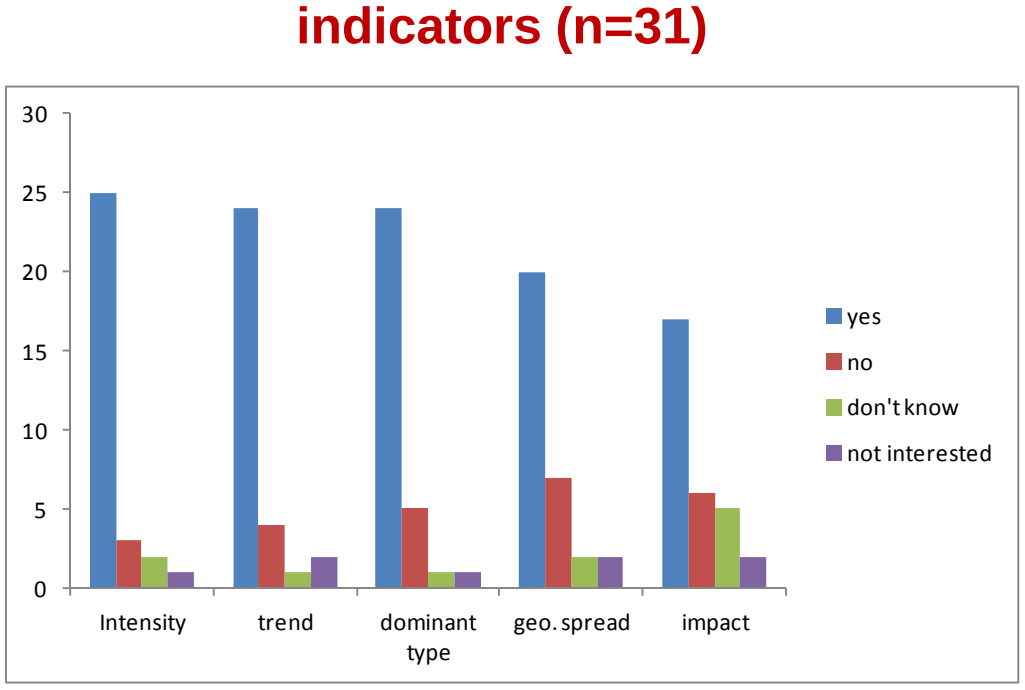
- Summarize the results for different methods used for the qualitative indicators in Europe
- This information was included in the proposal to quantify qualitative indicators

The proposal was presented at the Working Group Meeting and the survey was carried out in April 2012 and presented at the ECDC/WHO EURO Joint Annual Influenza

Surveillance (30 May-1June) and the Annual WHO Influenza Surveillance Meeting for NIS in September 2012

Summary of the results of the survey:

Interest in quantification of qualitative indicators (n=31)



- 31 surveys completed by 30 countries
- The majority of countries are interested in the quantification of the indicators: intensity, trend and dominant type in particular (77-80%).
- 11 countries (35%) use some form of method to quantify the intensity
- Output needs to be taken into account in defining the proposal for quantification of the qualitative indicators

4.4 WHO/ECDC expert meeting on qualitative indicators for influenza surveillance Copenhagen, Denmark, 9-10 May 2012

The objectives of this meeting were to review the definitions for the qualitative indicators (intensity, trend, geographic spread, dominant virus and impact), define the use and usefulness of the indicators, discuss a proposal for quantifying selected indicators including automated calculations, and provide input on the need for revisions including modification of current definitions, and possibility for (semi)-quantification of each of the indicators (Appendix 2).

4.5 Joint WHO/ECDC annual meeting presentation and discussion. Warsaw, Poland 30 May-1 June 2012

In the Joint WHO/ECDC annual meeting were included two presentations on qualitative indicators, one in the epidemiology working group and the other in the virology working group whose results were reported at the end of the meeting:

- Qualitative indicators and report on the recent Copenhagen meeting (Tomas Vega, Caroline Brown, Angus Nicoll)

- Dominant virus reporting and an overview of virological testing in the Region (Caroline Brown)

4.6 WHO Regional Office for Europe Annual Meeting on Influenza Surveillance for Eastern European Countries. Riga, Latvia 11-14 September 2012

In this meeting, the main conclusions of the WG were presented and discussed with the country representatives.

Results from the WHO/Europe/ECDC working group on qualitative indicators were presented (*A. Tomas Vega Alonso and Tamara Meerhoff, Temporary Advisers to WHO*).

4.7 Analysis of European data

European data from 19 countries were used to calculate QI by different procedures, according the reviewed definitions and methods and the suggestions and conclusions from the WG meetings and the recommendations taken from the Annual Influenza meetings.

We estimated the intensity, the trend and the dominant virus per country and per season and assessed the validity of these indicators to fit the necessities of the countries and the European surveillance systems.

5 Results

5.1 Data analysis

5.1.1 Intensity

Intensity. Methods

- Data from 22 countries:
  - EU and non EU countries
  - ILI and ARI weekly incidence data. 5-15 seasons per country

- Calculations:
  - MEM
    - Epidemic threshold estimated with the pre-epidemic period rates
    - Intensity thresholds estimated with the epidemic period rates
      - 40%, 90% & 97.5% upper CI of the Geometric mean
      - 90% & 97.5% upper CI of the Geometric mean
  - Percentiles
      - p50, p70, p85, p99
      - p50, p70, p95, p99

Different countries and different surveillance systems show different thresholds rates which refer to similar intensity levels.

MEM intensity levels

Epidemic thresold rate and 2/3 intensity thresolds defining 4/5 intensity levels

Country	*Epidemic thr.*	*40% thr.*	*90% thr.*	*97.5% thr.*
ILI - Belgium	144	507	903	1165
ILI - Castilla y Leon	69	264	738	1162
ILI - England	16	37	85	122
ILI - Greece	176	412	587	687
ILI - Hungary	150	396	668	842
ILI - Ireland	33	63	159	239
ILI - Israel	60	124	310	463
ILI - Norway	75	176	370	514
ILI - Poland	119	186	549	886
ILI - Portugal	27	63	180	286
ILI - Romania	234	311	712	1027
ILI - Serbia	104	169	319	422
ILI - Slovenia	28	118	276	402
ILI - Spain	80	205	511	765
ILI - Switzerland	73	307	492	606
ILI - The Netherlands	62	118	282	415
ARI - Albania	448	507	598	644
ARI - Kazakhstan	197	325	503	610
ARI - Kyrgyzstan	74	138	312	447
ARI - Romania	73	126	290	419
ARI - Russian Federation	699	869	1190	1368
ARI - Ukraine	927	774	1158	1384

MEM, with 5 levels (including baseline), produces a better distribution of the intensity reached by the historical seasons in Europe than the percentiles method

Distribution of the intensity levels with MEM and percentiles

(5-15 seasons in 22 countries)

MEM 4 levels (3 thr.)	% ILI seasons	% IARI seasons	
% Baseline	3.9	13.3	Epidemic Thres.
% Medium	79.9	60.0	90% Threshold
% High	11.2	11.1	97.5% Threshold
% Very High	5.0	15.6	

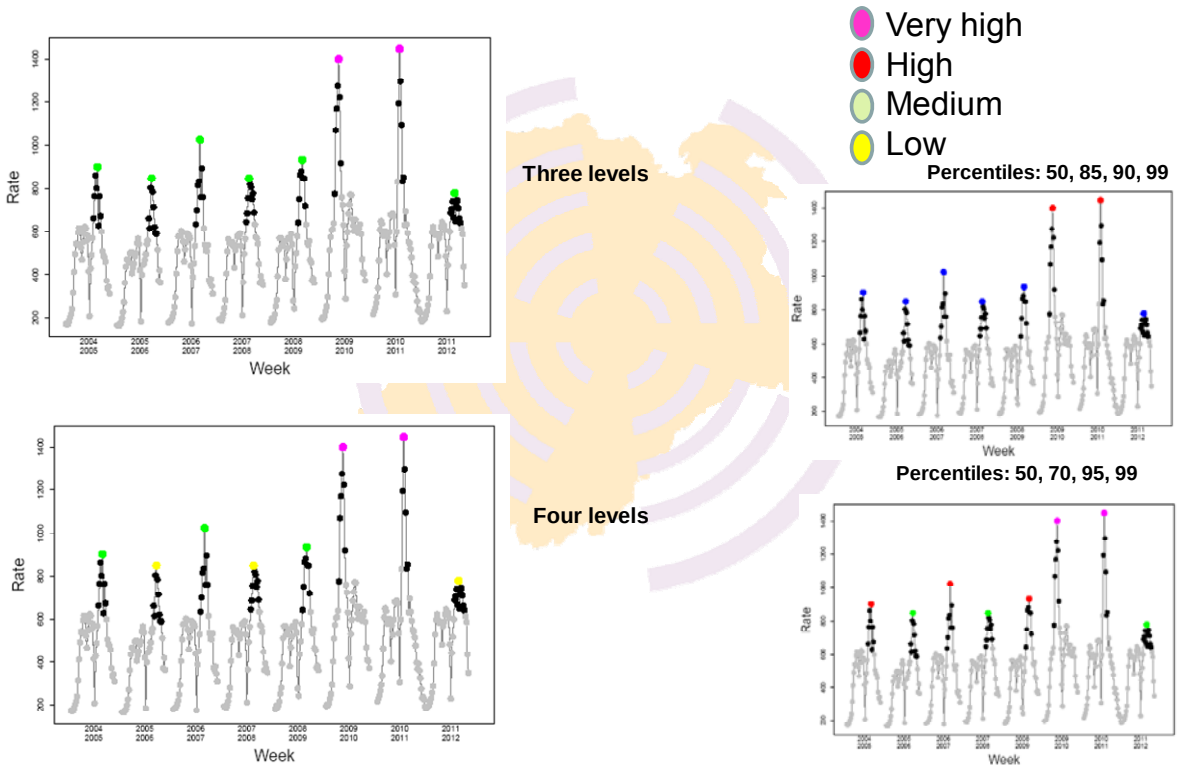
PERCENT. 5 levels	%-ILI seasons	%-IARI seasons	
% Baseline	0	0	p.50
% Low	1,7	0	p.85
% Medium	5.6	8.9	p.90
% High	70.4	66.7	p.99
% Very High	22.3	24.4	

MEM 5 levels (4 thr.)	%-ILI seasons	%-IARI seasons	
% Baseline	3.9	13.3	Epidemic Thres.
% Low	24.0	22.2	40% Threshold
% Medium	55.9	37.8	90% Threshold
% High	11.2	11.1	97.5% Threshold
% Very High	5.0	15.6	

PERCENT. 5 levels	%-ILI seasons	%-IARI seasons	
% Baseline	0	0	p.50
% Low	1.7	0	p.70
% Medium	41.9	37.8	p.95
% High	34.1	37.8	p.99
% Very High	22.3	24.4	

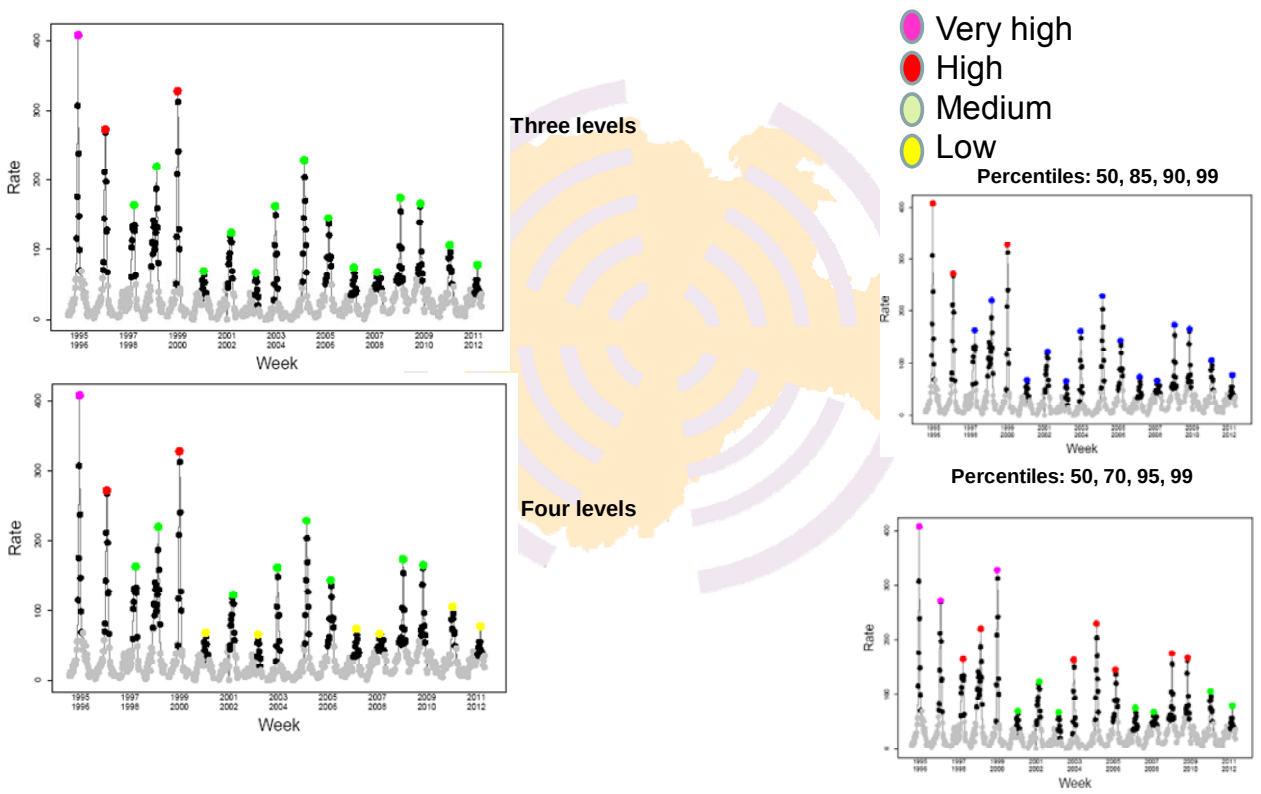
MEM , with four levels of intensity (5 with baseline) detects small differences of intensity among ARI seasons.

Examples MEM intensity levels (ARI).



MEM , with four levels of intensity (5 with baseline) detects better the differences of intensity among ILI seasons than other methods.

Examples MEM intensity levels (ILI).



MEM , with 5 levels produces a more descriptive display

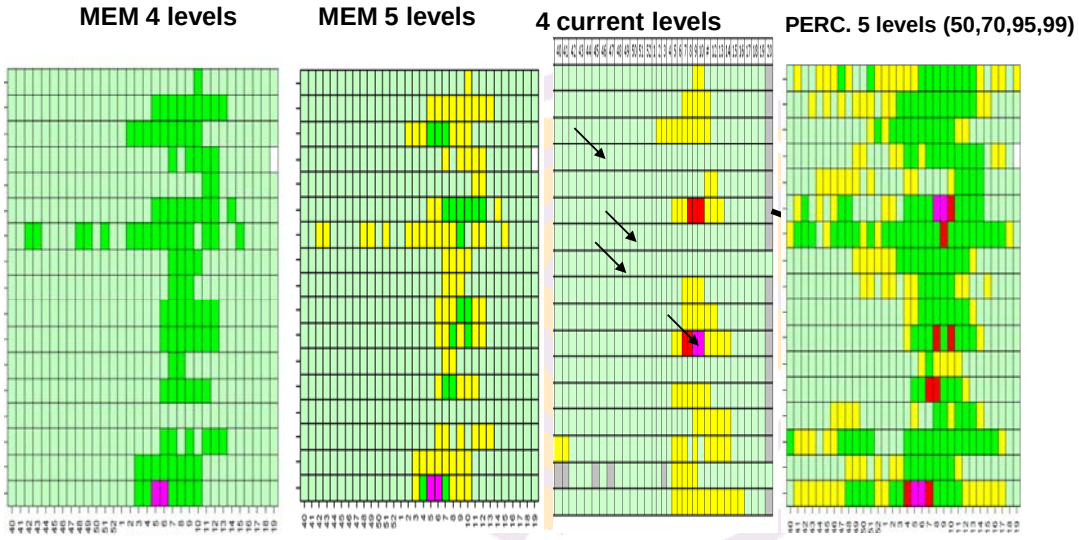
World Health Organization
REGIONAL OFFICE FOR Europe

Intensity levels 2011/12

ecdc

EuroFlu/ECDC

MEM 4 levels | MEM 5 levels | 4 current levels | PERC. 5 levels (50,70,95,99)



- Very high
- High
- Medium
- Low

Annual Influenza Meeting. Warsaw, Poland
30 May – 1 June 2012

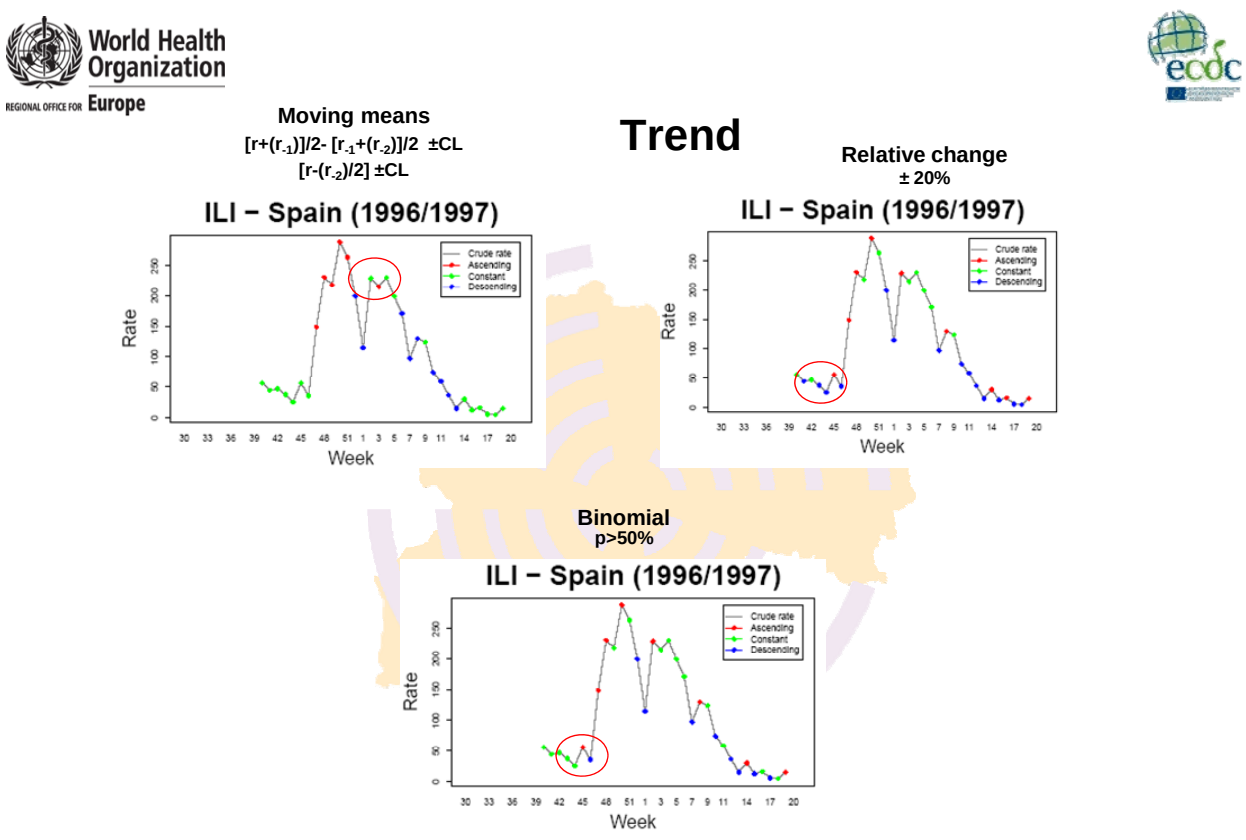
5.1.2 Trend

Trend. Methods

- Data from 22 countries:
  - EU and non EU countries
  - ILI and ARI weekly incidence data 5-15 seasons per country
- Calculations:
  1. Absolute difference between two consecutives rates and CI of the difference (using the historical data).
  2. Moving means differences = absolute difference between two rates r and (r-2) and CI of the difference (using the historical data).
  3. Relative change of two consecutive weekly rates (>20%).
  4. Binomial test of two consecutive rates (p>50%).
  5. Algorithm combining 1. and 2.

Annual Influenza Meeting. Warsaw, Poland
30 May – 1 June 2012

The ping-pong effect appears with any method.



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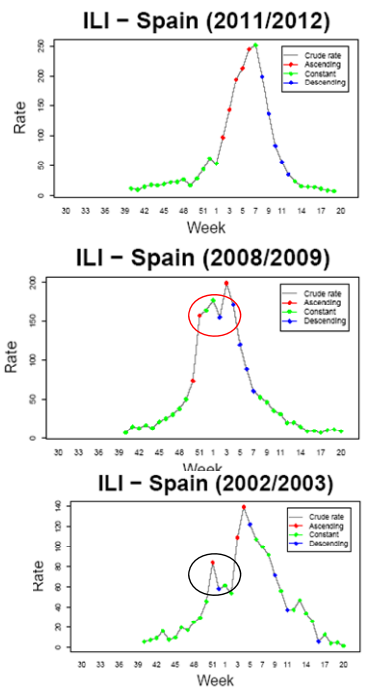
30 May – 1 June 2012

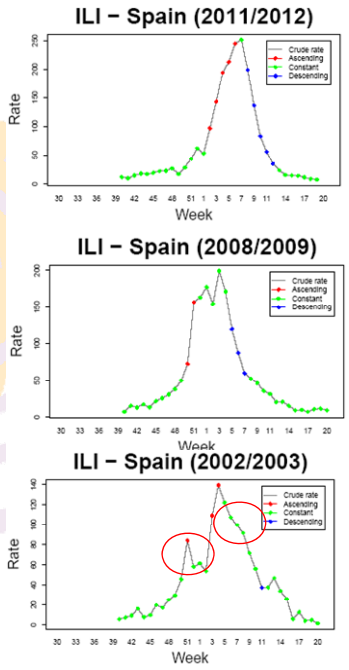
These methods, including absolute differences and CL, seem to minimize the ping-pong effect without affecting the sensitivity to detect changes in trend.

Trend

Absolute differences
$[r-(r_{-1})] \pm CL$



Algorithm combine absolute differences an moving means



5.1.3 Virus dominance

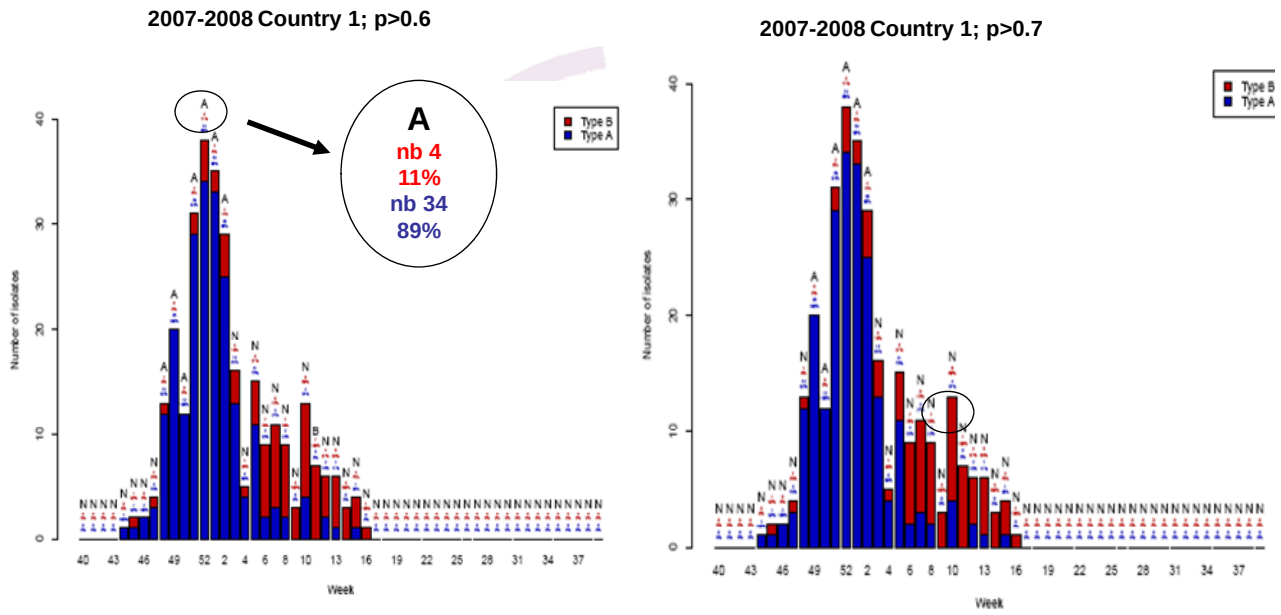
Virus type/subtype dominance. Methods

- Data from 3 countries:
  - 5 seasons
  - Number of virus type detection by week
- Calculation:
  - Binomial test
  - Two hipothesys:
    - p>0.6; 1-p<0.4
    - p>0.7; 1-p<0.3
- Sentinel vs. non sentinel samples

The figures displayed by week are: Dominant virus, number and percentages of detections by virus type/subtype.

Virus type/subtype dominance

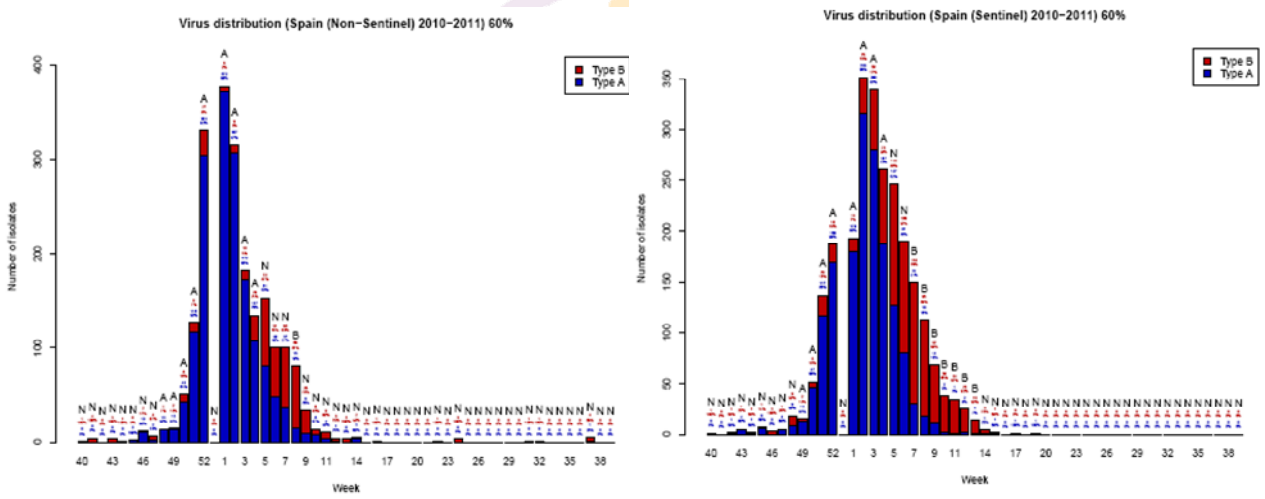
60% vs 70% dominance



It is possible to detect differences between sentinel and non sentinel samples, more important in some countries depending of their surveillance system.

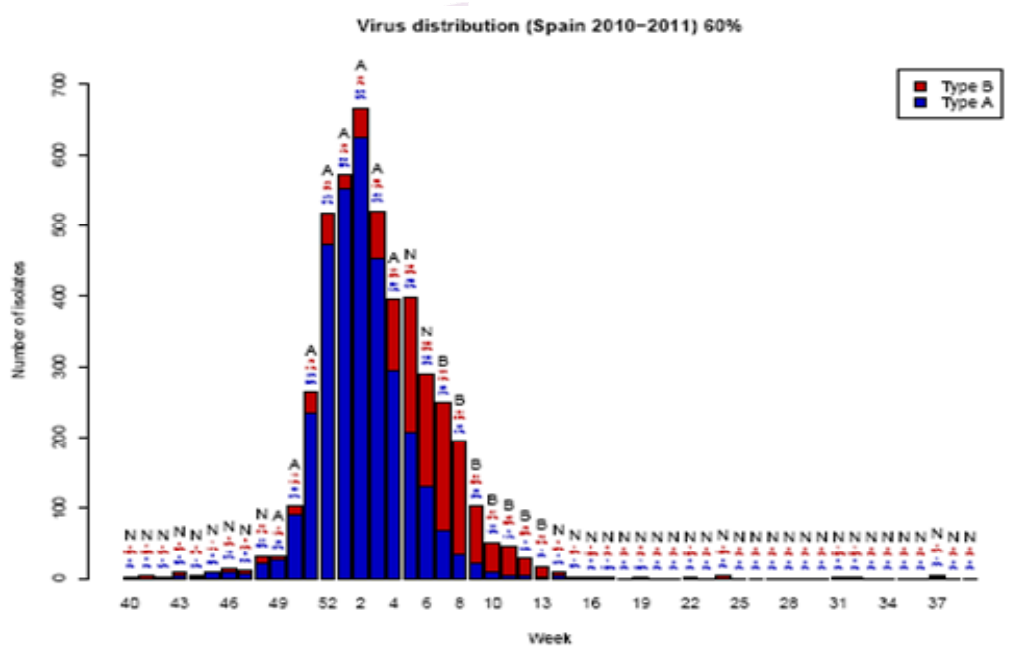
Virus type/subtype dominance

sentinel vs. non sentinel



Virus type/subtype dominance

Spain 2010-2011; p>0.6



5.2 Draft scheme for the implementation of qualitative indicators in EuroFlu/TESSy

As a result of this process of analysis of data and discussion into the working group and the outcome of the Annual Meetings on Influenza surveillance in Europe, a final report was issued (Appendix 3).

According the conclusions of this report, a scheme for the implementation the intensity, trend and dominant virus was prepared for piloting during the season 2012-2013.

DRAFT DOCUMENT
Health Management, Government of Castilla y León
Valladolid , July 2012

INTENSITY

METHODOLOGY

MEM is used to calculate the epidemic threshold and the three thresholds which define the intensity levels: medium, high and very high.

- All the countries in EuroFlu with 5 -10 seasons available.
- Countries with less than 5 seasons with a warning about the reliability of the results.

The results will be sent to the country representatives.

- Example data sent to country representatives:

SPAIN	Level
Epidemic Threshold	69
Medium Threshold	110
High Threshold	245
Very High Threshold	411

IMPLEMENTATION

Platform

To enter the thresholds in the platform, two methods are available:

- Manually: the country representative sets country's own thresholds in the website, calculated by any method.
- Automatically (default): Using data from the table previously sent to the Euroflu and stored in the platform.

In any case, country representatives could freely change their own epidemic or revert to the default levels.

Pilot Study

During the pilot study, data will be sent to EuroFlu in order to be used for reports in the platform.

- Example data sent to Euroflu:

Country	Epidemic Threshold	Medium Threshold	High Threshold	V. High Threshold
Spain	53	100	200	350
Belgium	120	…	…	…
Portugal	…	…	…	…
Montenegro*	…	…	…	…
				*less than 5 seasons in the model

Automatic calculation

Current weekly rate is compared to the thresholds and the intensity level, although not publicly available, can be viewed under compile maps and graphs and the Bulletin creation procedure. Participating countries are updated weekly on the reported intensity and the automated MEM intensity by email.

- Baseline level: under the epidemic threshold
- Low level: between the epidemic and the medium threshold
- Medium level: between the medium and the high threshold
- High level: between the high and the very high threshold
- Very high level: above the very high threshold

Graphical display

The thresholds could be also displayed in the graphs (only the epidemic threshold in some countries are displayed so far)

TREND

WARNING: This section is under heavy development. Methodology could be changed, implementation probably won't.

METHODOLOGY

MEM is used to determine the epidemic periods. Alternatively, countries can decide to use other methods available (based on epidemiological or virological data) or their own experience to determine the start and the end of the epidemics.

The differences of two consecutive weeks are calculated.

$$\Delta_i = r_i - r_{j-1}$$

- When $\Delta_i > 0$ it is said to be an *increment* in the weekly rate.
- When $\Delta_i < 0$ it is said to be a *decrement* in the weekly rate.

With all the *increments* of all epidemic periods a one-side confidence interval (95%) is calculated (the use of the geometric mean is recommended).

$$[\delta, +\infty)$$

With all the *decrements* of all epidemic periods a one-side confidence interval (95%) is calculated (the use of the geometric mean is recommended).

$$(-\infty, \eta]$$

Definitions:

Increasing: Weekly rates crossing up the epidemic threshold and all increments inside the epidemic period greater than δ.

Decreasing: Weekly rates that cross down the epidemic threshold and all the decrements (as a negative number) in the epidemic period lesser than η.

Stable: Weekly rates that are neither increasing or decreasing and weekly rates below the epidemic threshold.

IMPLEMENTATION

Pilot Study

Consultants will send the indicators to be used in the platform.

Automatic calculation

For each country, there are two additional indicators to be calculated each year: increment and decrement indicators. This could be done automatically and could be stored in a table along with the threshold value.

Also, the platform can calculate automatically the trend by using the following algorithm.

Algorithm

Calculate the current rate,

- Lower or equal than the epidemic threshold, the trend is *stable*.
- Above the epidemic threshold,
  - Any rate crossing the threshold: increasing/ decreasing
  - Calculate the difference between the current and previous rate.
    - If it is an increment,
      - Higher or equal than δ , the trend is *ascending*.
      - Lower than δ , the trend is *stable*.
    - If it is a decrement,
      - Lower or equal than η , the trend is *descending*.
      - Higher than η , the trend is *stable*.

Graphical display

Each week the trend is displayed in the weekly report table:

- Increasing.
- Decreasing.
- Stable (Unchanged).

DOMINANT VIRUS

METHODOLOGY

Once the number of positive swabs is entered in the website and the type and subtype are registered, an exact binomial test is calculated.

For each country weekly:

- A=Number of A type viruses isolated this week.
- B=Number of A type viruses isolated this week.
- P=A/A+B (A type virus percentage).

Binomial test hypothesis: P>0.60 and P<0.40.

- Rejecting P>0.60 leads to A dominance.
- Rejecting P<0.40 leads to B dominance.
- No rejection leads to co-dominance.

These calculations are done in the background each two/three weeks and are compared the results recorded by the country.

Note 1: The test can be used to compare A and B for the whole seasons, using the cumulated A and B type viruses (instead of using only the isolations of the current week).

Note 2: Also, the test can be used to compare H1 and H2, but the power of the test will decrease as there are fewer observations.

IMPLEMENTATION

Pilot Study

It is recommended that the platform perform automatic calculations each week, but it case it is impossible, calculations could be done by consultants in a month by month basis.

Automatic calculation

Each week the binomial test could be calculated by the platform to see if there is any significant difference between virus types.

Graphical display

Each week the dominant virus is displayed in the weekly report table.

Example of a report.

Country	Current Week dominant type	Season dominant type
Spain	Type B	Type A, subtype H3N2
Belgium		
Portugal		
Montenegro		

A final recommendation for using MEM in 2012-2013 season can be found in Appendix 4. A new version of the mem R library (v1.2) is available since the 1st of January, 2012

6 Conclusions

- Qualitative indicators are considered useful in flu surveillance (by extension, in the surveillance of other acute respiratory infections).
- Current Qualitative Indicators are subjective to interpretation, difficult the comparability among countries and produce inconsistencies with the quantitative indicators.
- Intensity, trend and dominant virus are priority in pilot testing of automated QI. Impact and geographical spread are also important but more difficult to implement.
- Using quantitative methods to estimate the intensity, to assess the trend and to evaluate the dominant virus will improve the comparability intra countries/regions (seasonally) and inter countries (geographically).
- The Moving Epidemic Method[9], as a general model of influenza epidemics, shows a good performance to estimate the intensity level of the ILI/ARI weekly consultation rates (as well as the seasonal accumulate rate)
- An algorithm for weekly assess the significant changes in the trend would be of interest at the European level.
- Dominant virus can only be evaluated, in a weekly basis, in countries with an important development of the virology surveillance. Seasonal cumulated dominance would be probably available in any country with a simple statistical test.
- More analysis and a better knowledge of the different Health Systems, data availability and usefulness at national and international level are necessary to harmonise the indicators of geographical spread and impact.

7 Recommendations

- To select volunteer countries: a minimum of 5 (ILI data), 3 (ARI data) and 4 (virological data) to be piloted.
- To monitor on a weekly basis three indicators during the season 2012-2013: intensity, trend and type/subtype virus dominance
- Evaluation of the pilot study: method and usefulness at the end of the 2012-2013 season.
- To improve the algorithms used in the pilot study.

In summary, the recommendations address to the standardization of the QI in ILI/ARI surveillance across Europe, the harmonization of weekly reports at international levels.

A guide for developing and implementing QI (and probably other indicators on flu surveillance) should be published.

8 Acknowledgements

Caroline Sarah Brown (WHO-Europe)
Pernille Jorgensen (WHO-Europe)
Ganna Bolokhovets (WHO-Europe)
Dmitriy Pereyaslov (WHO-Europe)
Angus Nicoll (ECDC)
René Snacken (ECDC)
Terry Gail Besselaar (WHO Headquarter)
Julia Fitzner (WHO Headquarter)
Kaat Vandemaele (WHO Headquarter)
Tony Mounts (WHO Headquarter)
Jan Kyncl (Czech Republic)
Silke Buda (Germany)
Siri Helene Hauge (Norway)
Dragana Dimitrijevic (Serbia)
Alla Miranenko (Ukraine)
Richard Pebody (United Kingdom)
Rod Daniels (United Kingdom)
Raul Ortiz de Lejarazu (Spain)
Marisol Rodriguez Pérez (Spain)
Carolina Rodriguez Gay (Spain)
J.A. Mott (CDC)
B. Nunes (Portugal)
Daniel Faensen (ECDC)
Flaviu Plata (ECDC)
John Paget (NIVEL)

To the primary health care professionals, for their dedication to the global influenza surveillance.

9 Appendix

9.1 Appendix 1: Working group meeting

World Health Organization
REGIONAL OFFICE FOR Europe

WHO expert meeting on qualitative indicators for influenza surveillance
Copenhagen, Denmark
9-10 May 2012

Original: English

Meeting venue
World Health Organization Regional Office for Europe
Scherfigsvej 8
2100 Copenhagen
Room T01, T-building

Preliminary Programme

Wednesday 9 May 2012

12:00-13:00	Registration of participants.
	A light lunch will be served during registration
13:00-13:10	Welcome and opening of the meeting *(Caroline Brown)*
13:10-13:20	Reporting of qualitative indicators for influenza surveillance in WHO European Region *(Pernille Jorgensen)*

13:20-13:30	Use of qualitative indicators from the global perspective, evaluation of their use during the pandemic *(Julia Fitzner)*
13:30-	*Review of the qualitative indicators – one-by-one* Presentation of current definitions of qualitative indicators *(Pernille Jorgensen)*, presentation of results of survey on qualitative indicators *(Tamara Meerhoff),* presentation and discussion of methods for quantifying qualitative indicators (*Tomas Vega*).
13:50-15:00	**Intensity**
15:00-15:30	*Coffee break*
15:30-16:15	**Trend**
16:15-17:00	**Geographical spread**
17:00-17:30	Summary of day 1
18:00-19:30	*Light dinner at WHO*

Thursday 10 May 2012

9:00-10:00	**Dominant virus**
10:00-10:45	**Impact**
10:45-11:15	*Coffee break*
11:15-12:45	Summarize recommendations on the need and options for revising qualitative indicators for influenza surveillance (including modification of current definitions, quantification, or semi-quantification)
12:45-13:00	Closure of the meeting *A "standing" lunch will be served after the meeting*

9.2 Appendix 2: Survey

Survey on
qualitative indicators

QUESTIONNAIRE 2012

Name respondent:	
Institute:	
Email:	
Country:	

World Health Organization - Regional Office for Europe

European Centres for Disease Control and Prevention

Please return this survey to: t.meerhoff@elg.umcn.nl

As a follow up of the Working Group Meeting on Qualitative Indicators at the Joint ECDC/WHO Regional Office for Europe meeting on influenza surveillance in June 2011, we would now like to assess how the qualitative indicators (e.g. intensity and trend) could be quantified in order to increase the robustness and accuracy of data reporting. To explore the various methods used in national influenza programmes, we would like to ask you to please complete the short questionnaire below. *Please note that the definitions used in TESSy/ EuroFlu are presented on page 4-6 after the survey questions.*

General questions about the surveillance system

What kind of data your surveillance system does weekly report to TESSy/EuroFlu? ☐ **ILI** ☐ **ARI** ☐ **Other**, ……

Source of data			
Sentinel system	☐	☐	☐
Nationwide/universal system	☐	☐	☐
Other, please specify	……	……	……
Denominator			
Cases per inhabitants	☐	☐	☐
Cases per consultations	☐	☐	☐
Other, please describe	……	……	……

Does your system/country have the number of notification sites (GPs, Health Centres etc.) reporting cases (including 0 cases) on a weekly basis?

☐ No, only aggregated information is available.

☐ Yes, information from each notification site is available.

Does your system/country estimate weekly incidence rates for smaller geographical areas (regions, provinces, etc.)?

☐ No, only aggregated information is available.

☐ Yes, information for smaller areas is available.

Intensity

Does your country use a definition to measure intensity levels (e.g. low, medium, high and very high)?

☐ No

☐ Yes, follows the (qualitative) EuroFlu and/or TESSy definition

☐ Yes, uses numeric (quantitative) thresholds for levels of intensity. Please provide below the threshold for the different levels used in the current influenza season:

Intensity	**ILI**	**ARI**
Low		
Medium		
High		
Very High		

Please briefly describe the method used to define the intensity levels:

……
……
……
……
……
……
……
……

Trend

Does your country use a definition to measure the trend?

☐ No

☐ Yes, follows the (qualitative) EuroFlu and/or TESSy definition

☐ Yes, uses another definition. Please describe the definition and, if available, the method below:

……
……
……
……

Dominant type

Does your country use a definition to measure the dominant virus type?

☐ No

☐ Yes, follows the EuroFlu and/or TESSy definition

☐ Yes, uses another definition. Please describe the definition and, if available, the method below:

……
……
……
……

Geographic spread

Does your country use a definition to measure the geographic spread?

☐ No

☐ Yes, follows the EuroFlu and/or TESSy definition

☐ Yes, uses another definition. Please describe the definition and, if available, the method below:

……
……
……
……

Impact

Does your country use a definition to measure the impact?

☐ No

☐ Yes, follows the EuroFlu definition

☐ Yes, uses another definition. Please describe the definition and, if available, the method

below:

.....

.....

.....

.....

Interest in qualitative indicators

Would you like EuroFlu/TESSy to implement standardized calculations for the 5 indicators that are currently defined qualitatively ? Please tick the boxes for each of the indicators below:

interest	**Yes**	**No**	**Don't know**	**Not interested**
Intensity				
Trend				
Dominant virus type				
Geographical spread				
Impact				

Comments

if you have any specific comments, please enter them here:

.....

.....

.....

.....

.....

.....

.....

.....

.....

.....

.....

THANK YOU!!!

Please see below the definitions of indicators of influenza activity

Intensity

- **Low**: no influenza activity or influenza at baseline* level
- **Medium**: level of influenza activity usually seen when influenza virus is circulating in the country based on historical data
- **High**: higher than usual levels of influenza activity compared to historical data
- **Very high**: influenza activity is particularly severe compared to historical data

* Baseline influenza activity is the level that clinical influenza activity remains in throughout the summer and most of the winter.

Trend

Trend refers to changes in the level of respiratory disease activity compared with the previous week.

- **Increasing:** evidence that the level of respiratory disease activity is increasing compared with the previous week.
- **Unchanged:** evidence that the level of respiratory disease activity is unchanged compared with the previous week.
- **Decreasing:** evidence that the level of respiratory disease activity is decreasing compared with the previous week.

Dominant influenza type

The current recommendations for reporting the dominant subtype are described below:

- The dominant type/subtype should be reported when 10 or more positive results for influenza type or subtype are available. In small countries or regions (e.g. countries/regions with a population of less than 5 million), the assessment can be based on a smaller number of positive results.

- If possible, the dominant type/subtype should be based on results available for the previous week. However, 1) at the beginning and end of the season, 2) in small countries/regions and 3) in countries where there are not so many samples, the assessment can be based on the previous TWO weeks.

- Definition of a dominant and co-dominant type:

  The threshold for dominance is set at 60% and the threshold for co-dominance is set at 40% / 60%.

Examples dominant type:	Report dominant type:
65% A and 35% B	only A
61% A and 39% B	only A

Examples co-dominant type:	Report dominant type:
60% A and 40% B	A + B
55% A and 45% B	A + B
50% A and 50% B	A + B

  If you want to report the H (and N) subtype of influenza A viruses in the dominant (sub)type, at least 50% of influenza A viruses should have been subtyped. Ideally, this means that a minimum of 20 influenza A viruses have been detected of which at least 10 were subtyped.

- Definition of a dominant and co-dominant influenza A subtype:

  If possible, there should be 10 influenza A subtypes to perform this analysis (however, points 1 and 2 above apply).

  The threshold for dominance is set at 60% and the threshold for co-dominance is set at 40% / 60%

Examples dominance:	Report dominant type:
65% A(H1N1)pdm2009 and 35% B	only A(H1N1)pdm2009
61% A(H1)pdm 2009 and 39% H3	only A(H1)pdm2009

Examples co-dominance:	Report dominant type:
60% A(H1N1)pdm and 40% A(H3N2):	A(H1N1)pdm2009 + H3N2

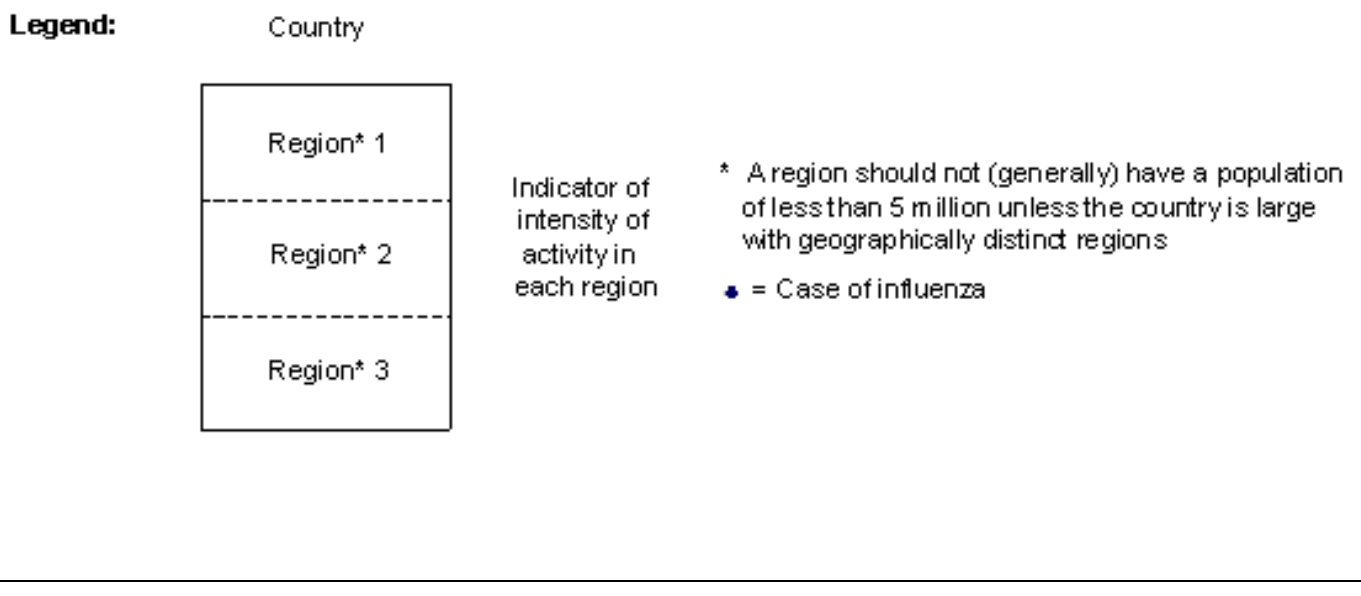
55% A(H1)pdm2009 and 45% H3:	A(H1)pdm2009 + H3
50% H3 and 50% B:	H3 + B
70% A(H1N1)pdm2009:	A(H1N1)pdm2009

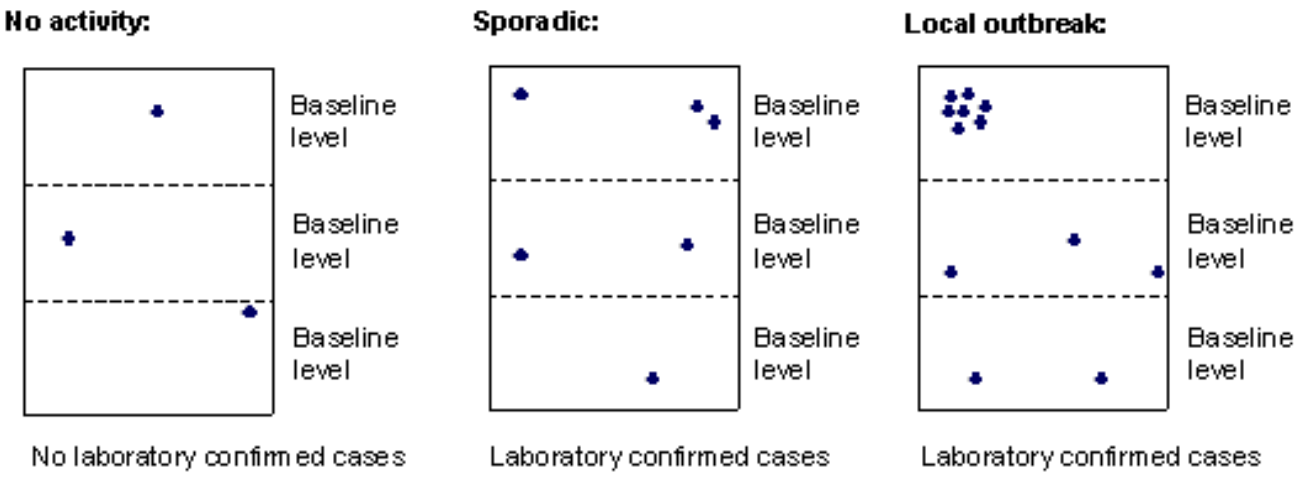
These are general rules and the national expert should take into consideration a number of factors (such as local outbreaks, holidays and geographical differences) when judging week-to-week developments. The national expert should apply these rules with an appreciation of special conditions, local knowledge and expertise.

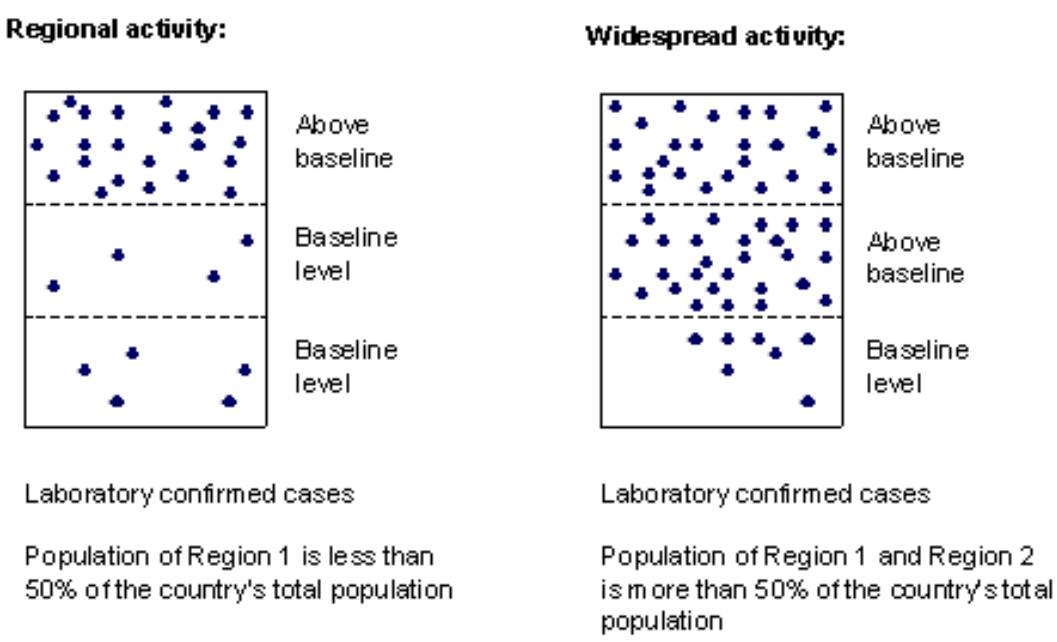
Geographical spread

- **No activity**: no laboratory-confirmed case(s) of influenza, or evidence of increased or unusual respiratory disease activity.
- **Sporadic** isolated cases of laboratory confirmed influenza infection in a region, or an outbreak in a single institution (such as a school, nursing home or other institutional setting), with clinical activity remaining at or below baseline levels.
- **Localized**: increased ILI/ARI activity in local areas (such as a city, county or district) within a region, or outbreaks in two or more institutions within a region, with laboratory confirmed cases of influenza infection. Levels of activity in remainder of region, and other regions of the country, remain at or below baseline levels
- **Regional**: ILI/ARI activity above baseline levels in one or more regions with a population comprising less than 50% of the country's total population, with laboratory confirmed influenza infections in the affected region(s). Levels of activity in other regions of the country remain at or below baseline levels
  This term is not (generally) to be used in countries with a population of less than 5 million unless the country is large with geographically distinct regions
- **Widespread**: ILI/ARI activity above baseline levels in one or more regions with a population comprising 50% or more of the country's population, with laboratory confirmed influenza infections.

The figures below present the geographical spread of influenza in a visual format.







Impact

Impact refers to the degree of disruption of health-care services as a result of acute respiratory disease.

- **Low**: demands on health-care services are not above usual levels
- **Moderate**: demands on health-care services are above the usual demand levels but still below the maximum capacity of those services
- **Severe**: demands on health care services exceed the capacity of those servicee

9.3 Appendix 3: Final report

WHO/ECDC expert meeting on qualitative indicators for influenza surveillance
Copenhagen, Denmark
9-10 May 2012

Original: English

Meeting venue
World Health Organization Regional Office for Europe
Scherfigsvej 8, 2100 Copenhagen

Meeting Report

Executive summary
The WHO Regional Office for Europe (WHO/Europe) and the European Centre for Disease Prevention and Control (ECDC) have established a working group (WG) to assess the feasibility and usefulness of quantifying the current qualitative indicators (QI) on influenza activity. The WG was established following an evaluation in 2011 of the performance of the four qualitative indicators (geographical spread, intensity, trend and impact), which showed that there were substantial differences in the interpretation of the indicators among countries, and discrepancies between weekly reported qualitative and quantitative data within countries.

A meeting was organized on 9-10 May 2012 to discuss options for improving the comparability of the indicators across the European countries and identifying efficient solutions for quantification of the indicators. The results of a survey sent to all member states in April 2012 on the use of the QI at country level were also presented and discussed.

The meeting concluded with a general agreement that there was interest in quantifying the QI, but there was some reservation to completely automate the calculation of the indicators on EuroFlu/TESSy. Feasibility, usefulness and simplicity should be evaluated for each of the different models with real data and automated calculation of some of the indicators should be piloted during the upcoming season (2012/2013).

The outcome of the QI WG meeting was presented at the annual joint WHO/Europe-ECDC meeting on influenza in Warsaw, 30 May-1 June 2012 (discussions and outcome of the meeting are available on the last page of this report) and will also be presented at the WHO/Europe annual influenza surveillance meeting for newly independent states in September 2012. Participants recommended to select a number of countries to participate in a pilot on quantifying the indicators intensity, trend and dominant virus (minimum of 5 countries with ILI surveillance, 3 countries with ARI surveillance, and 4 with virological data), and to evaluate the methods and usefulness at the end of the 2012-2013 season.

Participants

Member states experts
Dr Jan Kyncl (Czech Republic)
Dr Silke Buda (Germany)
Dr Siri Helene Hauge (Norway)
Dr Dragana Dimitrijevic (Serbia)
Dr Alla Miranenko (Ukraine)
Dr Richard Pebody (United Kingdom)

WHO Influenza Centre, United Kingdom
Dr Rod Daniels

ECDC
Prof. Angus Nicoll

WHO Regional Office for Europe
Dr Caroline Sarah Brown
Ms Pernille Jorgensen
Dr Ganna Bolokhovets
Dr Dmitriy Pereyaslov
Dr Tamara Meerhoff (consultant)
Dr A. Tomás Vega Alonso (consultant)

WHO Headquarter
Dr Terry Gail Besselaar
Dr Julia Fitzner, Dr Kaat Vandemaele and Dr Tony Mounts participated in the meeting from Geneva.

Chairs: Caroline Brown (Wed), Angus Nicoll (Thu)
Rapporteur: Tamara Meerhoff, Pernille Jorgensen

Background

The WHO Regional Office for Europe (WHO/Europe) and the European Centre for Disease Prevention and Control (ECDC) have established a working group (WG) to assess the feasibility and usefulness of quantifying the current qualitative indicators (QI) on influenza activity. This WG was established following an evaluation in 2011 of the performance of the four qualitative indicators (geographical spread, intensity, trend and impact), which showed that while the large majority of countries report on the qualitative indicators weekly during the influenza season, differences in the interpretation of the indicators among countries are common and discrepancies between weekly reported qualitative and quantitative data are often observed.

A meeting was organized on 9-10 May 2012 to discuss options for improving the comparability of the indicators across the European countries and identifying efficient solutions for quantification of the indicators. The results of a survey sent to all member states in April 2012 on the use of the QI at country level, including methods for quantification used, were also presented and discussed.

Objectives

The objectives of this meeting were to review the definitions for the qualitative indicators (intensity, trend, geographic spread, dominant virus and impact), define the use and usefulness of the indicators, discuss a proposal for quantifying selected indicators including automated calculations, and provide input on the need for revisions including modification of current definitions, and possibility for (semi)-quantification of each of the indicators.

Review of the qualitative indicators

The following aspects of the qualitative indicators were presented: current definitions, reporting problems, results of a region-wide survey on the use of qualitative indicators in countries, and possible methods for quantifying the indicators.

1) INTENSITY

The main comments and results of the discussions on the intensity indicator are summarised below.

Current definition	**Low**: no influenza activity or influenza at baseline* levels **Medium**: usual levels of influenza activity **High**: higher than usual levels of influenza activity **Very high**: particularly severe levels of influenza activity * Baseline influenza activity is the level that clinical influenza activity remains in throughout the summer and most of the winter.
Comments definition	• The definition includes a comparison with historical data and can therefore be quantified. • The intensity indicator is currently very subjective to interpretation. A standard method would enable standard inter-country comparisons. • The definition specifies that intensity is measured relatively to previous seasons, however, many countries use intensity as a measure of the progress of the influenza epidemic within a season.

- The intensity definition was found difficult to interpret. The indicator is a measure of consultation rates for ILI or ARI and depends on influenza activity but also on health seeking behaviour which varies substantially between countries and over time.
- The term intensity suggests some measure of severity or impact, but actually reflects the influenza activity measured by the number of new cases with ILI or ARI per 100.000 population.
- The definition is not very specific as it is includes terms such as: ‘usually seen’, ‘baseline level’, ‘particularly severe’, and ‘historical data’.
- The definition also includes the wording “influenza activity”, but it does not specify if this covers clinical activity (ILI or ARI), virological activity or both.
- The definition states that low intensity equals "no activity". This is considered to be incorrect.
- Finally, the term "respiratory disease activity" may be more appropriate than "influenza activity" if intensity is based on clinical consultation rates only.

Use and usefulness

The intensity indicator is used:

- At the inter-country level to show in which countries influenza season has started and the intensity level reached.
- At country level to show what the current levels of ILI/ARI are compared with historical data or within an influenza season.

The intensity indicator is primarily used for reporting to EuroFlu/TESSy and to a lesser extent at country level for the national report.

Reporting problems

Intensity is most consistently reported among all indicators (i.e. no ping-pong reporting during an influenza season). Reported intensity levels, however, do not always match the quantitative data on ILI and/or ARI and sometimes no or limited historical data are available which makes application of the definition difficult.

For example during the 2011-2012 influenza season a number of countries reported “high” or “very high” influenza activity, although influenza rates were not higher when compared with historical data. This may reflect a tendency to interpret ‘intensity’ as a measure of the progress of the seasonal influenza epidemic and not as a measure of the intensity of the season compared to previous seasons.

Adjustment of definition required?

There was a general agreement that the definition of the indicator lacked clarity and that adjustment would be useful. Different options were discussed.

- Simplify and reduce the number of intensity levels to 3-4 and exclude the "very high" level. *(Note: this may lead to a loss of information)*
- Clarify what ’intensity’ is measuring: virological activity, clinical consultation rates or both. To simplify it was suggested to define ‘intensity’ as a measure of the incidence of ILI or ARI.
- Change the wording: use the word "exceptional" instead of high/very high; use the word "moderate" or "ordinary" instead of medium.
- Rename "Intensity" to "Activity", this better reflects what is being presented.
- Define intensity in terms of % positive or combine the % positive and clinical activity. *(Note: % positive differs by country and can change over time, this option would need to be assessed first).*
- Consider using a pre-defined distribution of levels in the definition (e.g. out of 10

seasons one would expect: 3 low, 5 medium, 1-2 high and 0-1 very high season).

Is quantification an option?

Yes, a number of methods currently exist to quantify “intensity”.

Another option, not meant to quantify, but to reduce inconsistent reporting is to link “intensity” to other qualitative indicators in the data entry forms on EuroFlu/TESSy (e.g. if “sporadic detections” (geographical spread) has been reported by a country, the country would not be able to report “no activity” (intensity).

The survey on QI showed that a total of 25 countries (n=31) were interested in quantification of the intensity indicator. Eleven countries have already developed intensity thresholds (2 based on MEM, 2 based on the percentiles method, 7 based on other methods).

Note: Automated calculations of intensity thresholds with either MEM or the percentiles method require renewed calculations of the thresholds each year unless the levels do not change significantly between seasons.

General comments

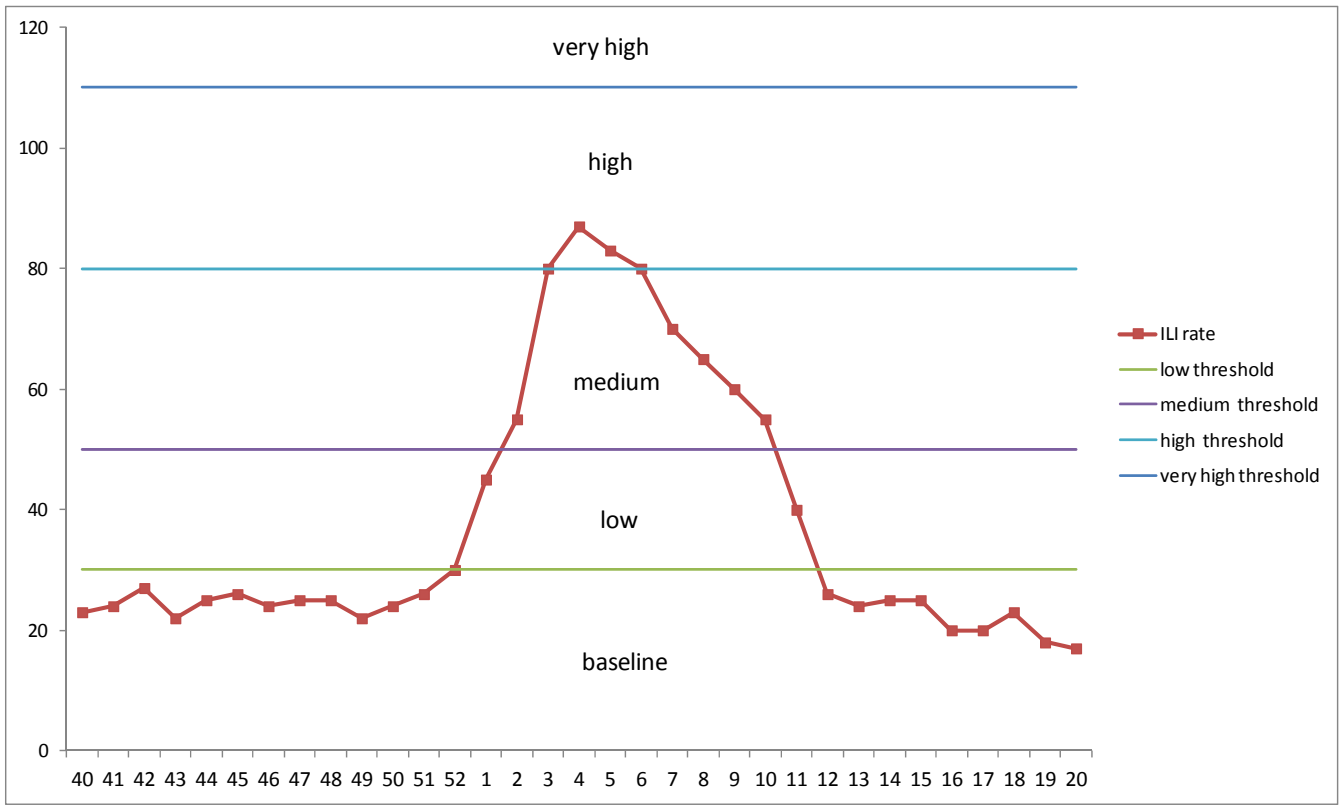
- A perfect method that fits all surveillance systems does not exist. However, if a reliable method could be implemented for a number of countries, this would greatly improve the comparability, increase the robustness of the data, and facilitate interpretation of the data.
- In ARI surveillance systems, virological information is required to define if there is influenza activity.
- Consider the use of age adjusted rates to define intensity levels if there are large differences between age groups represented in the surveillance system.
- If automatic calculations are implemented on EuroFlu/TESSy, each country should have the option to over-write the data in case of disagreement.

Draft proposal to the annual meeting

<u>Definition</u>
Intensity: measure of the incidence of ILI/ARI

<u>Levels and criteria</u> (see figure)

1. At baseline level: Below the epidemic threshold (MEM)
2. Low: Between the epidemic threshold and the medium threshold
3. Medium: Between medium threshold and the high threshold
4. High: Between the high threshold and the very high threshold
5. Very high: Above the very high threshold



Pilot monitoring season 2012-2013

- Minimum of 8 countries (5 ILI/ 3 ARI)
- Weekly monitoring of the intensity in pilot countries
- Final evaluation end of season

2) TREND

Current definition	Trend: changes in the level of the ILI/ARI incidence rate compared with the previous week. **Increasing:** evidence that the level of ILI/ARI rate is increasing compared with the previous week. **Unchanged:** evidence that the level of ILI/ARI rate is unchanged compared with the previous week. **Decreasing:** evidence that the level of ILI/ARI rate is decreasing compared with the previous week.
Use and usefulness	• The definition is clear, but would be more robust if trend in ILI or ARI would be based on previous *two* weeks instead of *one*. • The trend indicator is used to compare ILI and/or ARI consultation rates to the previous week. Most countries at the WG meeting consider both the ILI or ARI rate and influenza detections or the positivity rate when determining trend. • Currently the indicator is mostly used at a regional level to report how many countries are observing increasing, decreasing or stable levels of ILI and/or ARI consultation rates. • Trend is also used to assess the progression of the epidemic and to detect unexpected changes which can indicate a new wave caused by other type or subtype in combination with virological data.
Reporting problems	The interpretation of the definition varies between countries and does not

always reflect clinical consultation rates. As the definition of trend takes only two data points into account it often leads to so-called “ping-pong” reporting. When consultation rates are low at the start of the season, often an increase is reported in one week and the next week a decrease is reported. While this complies with the definition, it is less informative as the purpose of the indicator is to understand the general trend in influenza activity rather than minor fluctuations.

Adjustment definition required?

No general agreement.

Options:

- Consider to include virological data.
- Consider to include the comparison to the previous *two* weeks *(Note: this is done in Switzerland).*
- Aggregate countries (for example Western Europe) and compare trends in different zones.

Is quantification an option?

Yes. A total of 24 countries (n=31) indicated interest in quantifying the trend indicator.

Options for quantification are:

- To define trend for two consecutive weeks
- To calculate rate change
- To calculate moving means

Two countries have established a rate change method to define the trend.

Can we pilot test in some countries?

Yes. But some participants of the working groups indicated some reservation with regard to the usefulness of a mathematical approach.

General comment

- A number of participants cautioned against making the indicator trend which is relatively simple, more difficult.

Draft proposal to the AM

<u>Quantification</u>
There are different options to quantify the trend indicator:

- Absolute differences (compare to previous week and previous two weeks)
- Changing rates
- Relative change of two consecutive weeks
- Moving means
- Algorithm combining absolute differences and moving means

The preferred method needs to be identified; the pilot testing will probably be carried out using two methods.

<u>Pilot monitoring season 2012-2013</u>

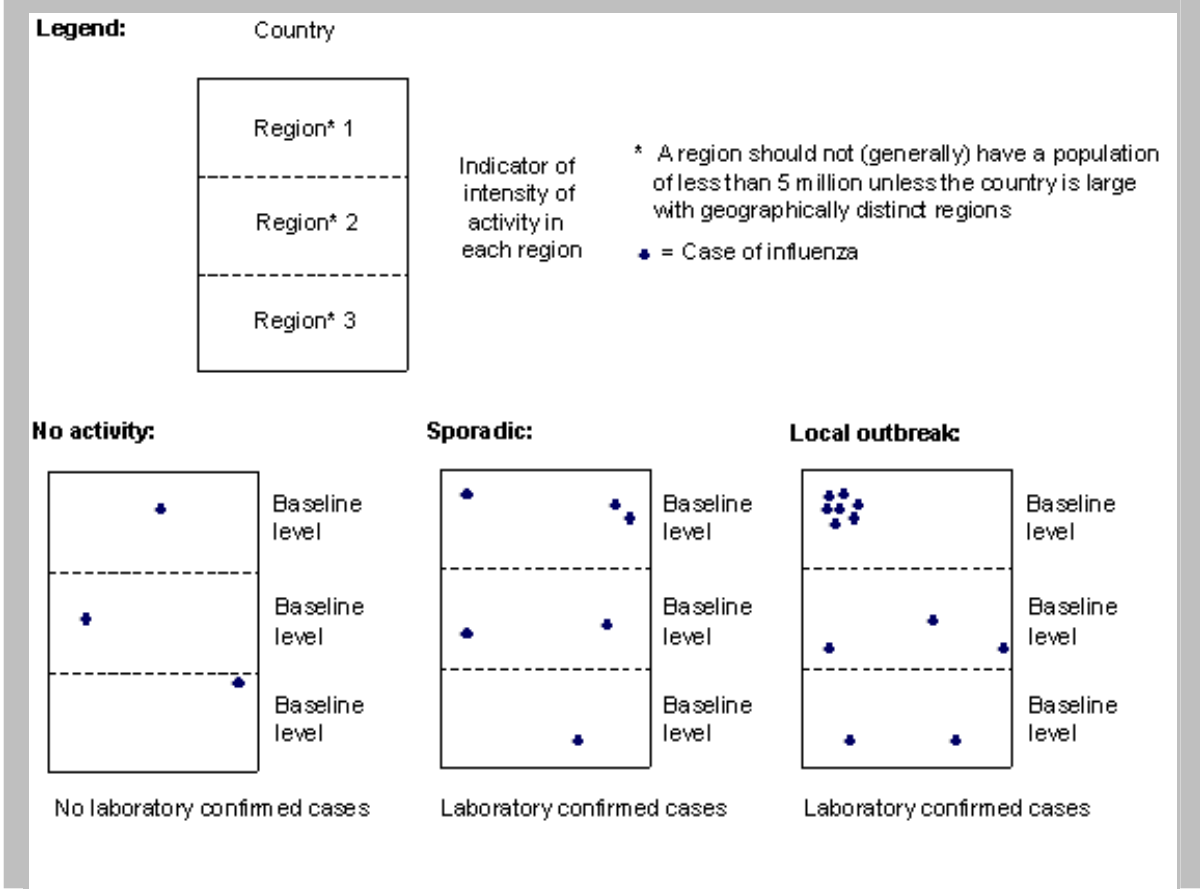
- Minimum of 6 selected countries (4 ILI/ 2 ARI)
- Weekly monitoring of the trend
- Final evaluation end of season

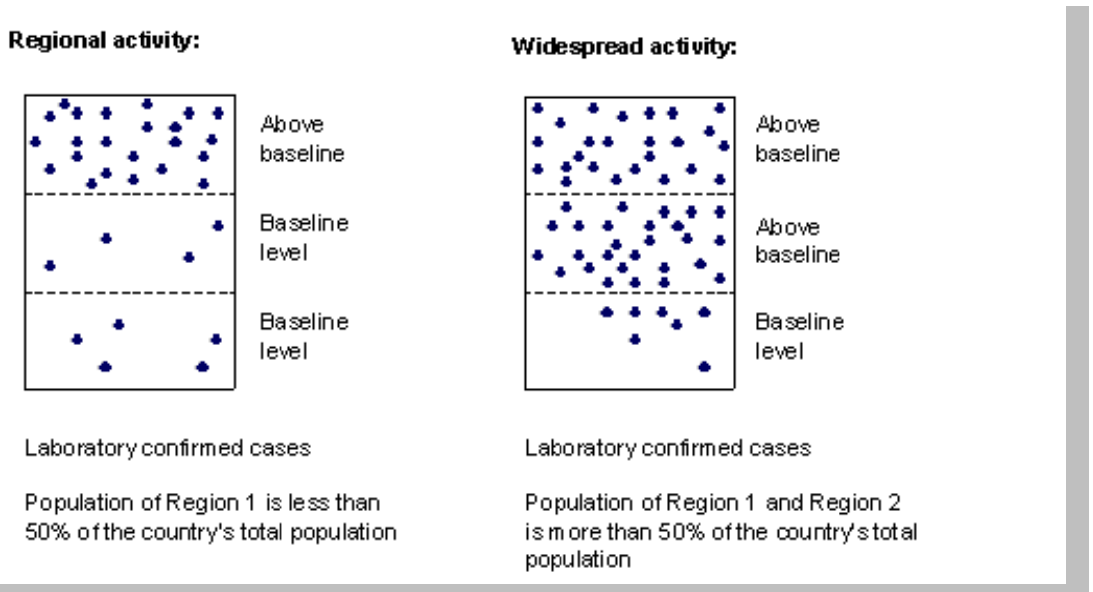
3. GEOGRAPHICAL SPREAD

Current definition

- **No activity**: no laboratory-confirmed case(s) of influenza, or evidence of increased or unusual respiratory disease activity.
- **Sporadic**: isolated cases of laboratory confirmed influenza infection*
- **Localized**: limited to one administrative unit of the country (or reporting site) only.
- **Regional**: appearing in multiple but <50% of the administrative units of the country (or reporting sites).
- **Widespread**: appearing in ≥50% of the administrative units of the country (or reporting sites).

The figures below illustrate the definitions of geographical spread



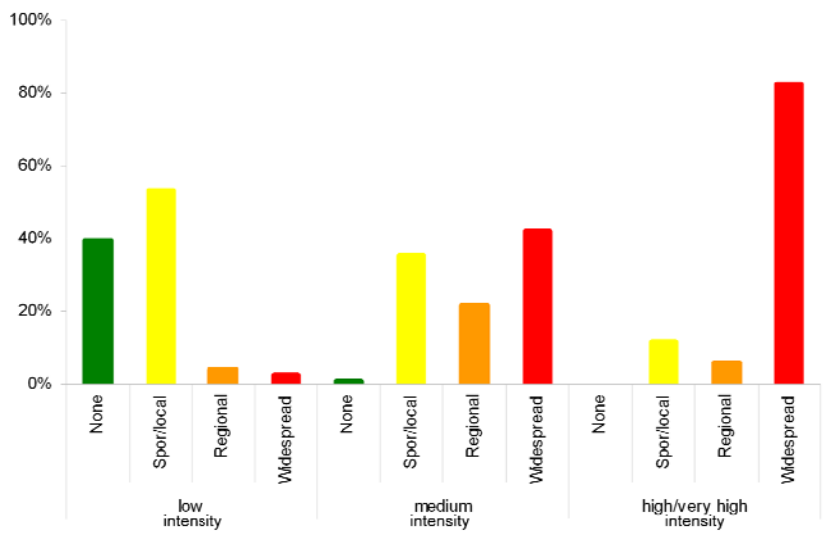


Use and usefulness

- The geographical spread indicator is mostly used for international reporting and comparison.
- The definition is generally considered to be complicated.
- Difficult to distinguish between local and sporadic activity as per the definition.
- The usefulness of this indicator depends on the size of the country ("regional level" should not be used in small countries).

Reporting problems

Inconsistencies between weekly reports of "geographical spread" and the indicators "intensity" and "laboratory confirmed influenza" respectively are frequently observed (see figure below). E.g. regional and widespread geographical activity (defined as ILI/ARI activity *above* threshold) is reported in weeks with low intensity (defined as ILI/ARI activity *below* threshold). Similarly, sporadic/local geographical activity is reported in weeks when high to very high intensity is reported.



Furthermore, "no activity" is often reported by countries in weeks where laboratory confirmed influenza is being detected.
It is potentially difficult to distinguish between local and sporadic activity as the distinction between the two definitions is subtle (outbreak in 1 institution versus 2 institutional outbreaks within a country).

Adjustment definition required?

Yes, the number of different levels may be reduced. For example no/sporadic activity, sporadic/local, or regional / widespread could be combined.

Is quantification an

Not decided.

option?

A total of 20 countries (n=31) indicated interest in quantifying the geographic spread indicator.

Options:

- Geostatistics and spatial analysis
- Automated check when submitting data to TESSy/EuroFluto exclude certain combinations of data entries (e.g. reporting of virological detections excludes the possibility to report no activity, or it would not be possible to report widespread and low intensity concurrently).

Can we pilot test in some countries?

Maybe/ Yes (not priority)

General comment

- Geographical spread in small countries and in large countries may not be directly comparable as small countries tend to report sporadic and widespread activity only, while larger countries often report on all levels throughout the season .
- One country (Switzerland) uses the % of GPs that report ILI and detections of influenza to determine levels of geographic spread. This method may be tested/applied in other countries.
- In the WHO global influenza report no distinction between sporadic and local activity is made.

4. DOMINANT VIRUS

Current definition

The dominant virus is defined as the influenza type (or sub/type) that is the most frequently detected in sentinel and non-sentinel specimens for a given week. The threshold for dominance is set at 60%.

The current recommendations for reporting the dominant virus are:

a) The dominant type/subtype should be reported when **10 or more positive results for influenza type or subtype** are available. In *small countries or regions* (e.g. countries/regions with a *population of less than 5 million*), the assessment can be based on a **smaller number** of positive results.

b) If possible, the dominant type/subtype should be based on results available for the **reporting week**. However, 1) *at the beginning and end of the season*, 2) *in small countries/regions and* 3) *in countries where few samples are tested*, the assessment can be based on the previous **TWO weeks**.

For examples and more information, please see the EuroFlu library on: https://www.euroflu.org/repository/documents/EuroFlu_Operating_Procedures_Manual_ver_3.pdf

Use and usefulness

- Most participants consider the definition to be clear.
- Countries monitor dominant virus reported by other countries to assess

if a second influenza wave (e.g. due to influenza B) can be expected within the season.

- Weekly data on dominant type may not be so informative (e.g. due to ping-pong reporting); it may be more useful to monitor virus dominance on a monthly overview.
- Concerning the reporting of dominant A and N-subtypes, 10 A or N-subtyped viruses are required for reporting dominant subtype virus. This is a challenge in countries which are mostly testing non-sentinel samples where subtype is often not determined.
- Some countries do not always use the rules of the definition, to avoid ping-pong reporting and some countries prefer to use a 70% threshold for dominance.
- If a large proportion of weekly influenza detections reported from a country come from a single outbreak/number of outbreaks, the reported "dominant virus" may misrepresent the general composition of viruses circulating in the country.

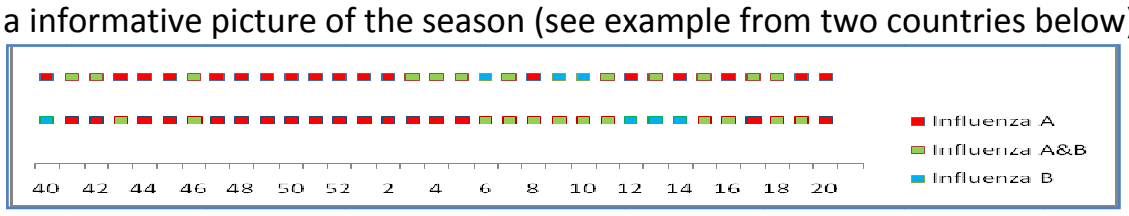
Reporting problems

The compliance with the definition is generally low, and during the 2010/2011 the definition of dominant virus was adhered to in only 60% of the reports.

Dominant type reported by country*	Dominant virus according to EuroFlu/TESSy definition			
	Dominant A	Dominant A&B	Dominant B	Total
None	38	23	26	87
Type A	209	8	2	219
Type A and B	70	76	34	180
Type B	3	22	94	119
Total	**320**	**129**	**156**	**605**
% weekly report complying with definition	**65.3%**	**58.9%**	**60.3%**	

*Based on all sentinel and non-sentinel outpatient samples where total number of positive samples is 10 or more per country per week

Furthermore, as only 10 detections are required to estimate virus dominance, weekly changes in reported dominant virus are common and may not give very a informative picture of the season (see example from two countries below)



Adjustment definition required?

- The current definition suggests that dominant type should be based on at least 10 detections. This is considered a low number. Some suggested that 40 detections would be more robust.
- The distribution of viruses needs to be assessed to define the dominant type (currently 40/60 is used). Data for previous seasons showed that influenza B rarely reach 40%.
- It is proposed to assess if virology data from sentinel and non-sentinel sources differ in order to determine if it is appropriate to include both sentinel and non-sentinel data in the calculation of dominant type.
- The precise objectives (e.g. to monitor dominance of viruses or to simply monitor which viruses are circulating) and significance of

	reporting dominant type also need to be assessed. This will help to formulate a clear definition of the indicator
Is quantification an option?	Yes. A total of 24 countries (n=31) indicated interest in quantifying the dominant type indicator.
Can we pilot test in some countries?	Yes, but the minimum number of detections needed to calculate dominant type should be assessed as well as the need to if sentinel and non-sentinel samples should be combined.
General comment	• Percentages of types and subtypes may be more interesting to present than "dominant type". • The dominant type is presently reported by week, a maybe better picture would be provided for a longer time period, e.g. 2 or 4 weeks. • *Note: This can cause problems because of the quickly changes in virus dominance: Miss of opportunity.* • Need to assess if there are differences between dominant type in sentinel and non-sentinel. • Some countries may not be able to report dominant type, as they test too few samples by week, this would support reporting dominant virus on a monthly basis
Draft proposal to the AM	<u>Definition</u> Dominant virus: The prevailing virus type (or subtype) over others with a threshold for dominance and co-dominance OR prevalent and co-prevalent. <u>Levels and criteria</u> 1. Dominance /Prevalence 2. Co-dominance/Co-prevalent <u>Quantification</u> • Automated one-tailed binomial test: >60% or >70% for dominance of A/B • Automated one-tailed binomial test: >60% or >70% for dominance of H1/H3

5. IMPACT

The impact indicator was not discussed in detail, but some results are presented below.

Current definition	**Low**: demands on health-care services are not above usual levels. **Moderate**: demands on health-care services are above the usual demand levels but still below the maximum capacity of those services. **Severe**: demands on health care services exceed the capacity of those services.

Use and usefulness	This indicator was not discussed in detail
Reporting problems	Impact has the lowest reporting completeness among the qualitative indicators (see figure below). The definition of “impact” is unspecific, making comparisons between countries difficult.
Adjustment definition required?	Not discussed
Is quantification an option?	Not known. Seventeen out of 30 countries are interested in quantifying the impact indicator Options: -Hospital admission surveillance -Visits to the Hospital Emergency department -Mortality surveillance -Intensive care unit surveillance
Can we pilot test in some countries?	Not discussed

Outcome of the Annual Meeting (AM) in Warsaw, 30 May - 1 June 2013

Quantification of qualitative indicators - Sessions 2a2 and 12b.

Present: Warsaw meeting participants.

A summary of the WG meeting and a suggestion for automated calculations for the indicators were presented at the Annual Meeting (AM) in Warsaw, 30 May-1 June 2012. The objectives were: 1) to inform on the progress of this project and preliminary results showing the feasibility to quantify the intensity, trend and dominant virus, and 2) to propose a pilot for the 2012-2013 season with selected countries.

The main conclusions reached at the AM were:

1. The majority of countries are interested in the quantification of the indicators: intensity, trend and dominant type in particular (77-80%).
2. The objectives for quantifying these indicators are to improve comparability between seasons and countries, to reduce inconsistencies and to simplify the display in the web platforms.
3. Intensity

   Options for quantification:
   a. The Moving Epidemic Method (MEM) with (4-)5 levels.
   b. An alternative, for countries not using MEM epidemic threshold, could be levels based in percentiles in the epidemic period.

   It is necessary to assess false alerts and take into account the virological information, particularly in countries reporting ARI.
4. Trend

   Options for quantification:
   a. Absolute difference between two consecutives rates at the 95% confidence level of the difference (using the historical data).
   b. Moving means differences = absolute difference between two rates r and (r-2) and CI of the difference (using the historical data).
   c. Relative change of two consecutive weekly rates (>20%)
   d. Binomial test of two consecutive rates.
   e. Algorithm combining options a and b.

   Important to keep the equilibrium between the longer perspective (2-3 weeks) and the capacity to detect quick trend changes. Assess the absolute differences vs. relative differences between two consecutive weeks.
5. Dominant virus

   Options for quantification:
   a. Binomial test; Two hypothesis: $p>0.6$; $1-p<0.4$ and $p>0.7$; $1-p<0.3$. 60% or more may be better than 70% to confirm the dominance of one virus type/subtype over the other.
   b. It is not necessary to establish a minimum number of swabs to determine the dominance. The statistical test takes into account the n and the % .
   c. We need to look if there are differences in virus dominance between sentinel and non-sentinel swabs.
   d. Equilibrium between detecting quick changes and having a wide picture of the dominance: dominance during 2-3 weeks.

The recommended next steps are:

- To select volunteer countries: a minimum of 5 (ILI data), 3 (ARI data) and 4 (virological data) to be piloted*.
- To monitor on a weekly basis the three indicators during the season 2012-2013: intensity, trend and type/subtype virus dominance.
- Evaluation of the pilot study: method and usefulness at the end of the 2012-2013 season.

* If possible the pilot testing will be performed on the EuroFlu platform for one or more of the indicators.

9.4 Appendix 4: Recommendations for using the Moving Epidemic Method during 2012/2013 season.

The epidemic threshold and the rest of intensity thresholds could be calculated using the Moving Epidemic Method (MEM); Vega & Lozano, Influenza and Other Respiratory Viruses, DOI:10.1111/j.1750-2659.2012.00422.x.

These recommendations are based on the goodness of the estimates calculated with data from 19 European countries, the discussions into the working group of experts (WHO-Europe/ECDC) and the conclusions obtained from several meetings on influenza epidemiology.

There is a library for the R Language, called 'mem', which makes the calculations automatically.

Number of seasons

To assess the stability of estimations it is recommended to use a minimum of 5 seasons of historical data to compute thresholds.

There are some countries that have reported problems when using old data, when the virus shows a significant trend over the years. To avoid these problems a maximum of 10 seasons is recommended.

Pandemic season 2009-2010

Some countries have reported problems when including the pandemic (2009/2010) season, showing a bimodal curve that affects the pre-epidemic information. So it is recommended not to use the pandemic in the calculations.

MEM program technical details

The parameters of the MEM to detect the epidemic period:

- Fixed criteria method - value by default in the v1.2 R library.
- Criteria: slope change of 2.8% or less - value by default in the v1.2 R library.

The parameters of the MEM to calculate the epidemic threshold:

- One-sided point confidence interval (using standard deviation) around the arithmetic mean - *value by default in the* v1.2 *R library*.
- Number of points per seasons used to calculate confidence intervals: $30/number\_of\_years$ - *value by default in the* v1.2 *R library*.
- Confidence level: 95% - *value by default in the* v1.2 *R library*.

The parameters of the MEM to calculate the intensity thresholds:

- One-sided point confidence interval (using standard deviation) around the geometric mean - *value by default in the v1.2 R library*.
- Number of points per seasons used to calculate confidence intervals: $30/number\_of\_years$ - *value by default in the v1.2 R library*.
- Confidence levels:
  - Medium threshold (MT) – 40% confidence interval (recommended) mean - *value by default in the v1.2 R library.*
  - High threshold (HT) – 90% confidence interval (recommended) - *value by default in the v1.2 R library*.
  - Very high threshold (VT) – 97.5% confidence interval (recommended) - *value by default in the v1.2 R library.*

Intensity levels

MEM produces the epidemic threshold and three intensity thresholds and establishes five intensity levels of influenza:

- Baseline level – No influenza or influenza **below the epidemic threshold**.
- Low level – An epidemic lower than normal. **Above the epidemic threshold and below the medium threshold**.
- Medium level – An average season. **Above the medium threshold and below the high threshold.**
- High level – A higher than expected season. **Above the high threshold and below the very high threshold.**
- Very high level – An abnormally high season. **Above the very high threshold.**

10 References

[1] Vega T, Lozano JE. Modeling influenza epidemic - can we detect the beginning and predict the intensity and duration? Int Congr Ser 2004;1263:281–283.

[2]WHO. Human infection with pandemic (H1N1) 2009 virus: updated interim WHO guidance on global surveillance (http://www.who.int/csr/disease/swineflu/guidance/surveillance/WHO_case_definition_swine_flu_2009_04_29.pdf). Accessed September 2012.

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[4]ECDC. Reports https://extranet.ecdc.europa.eu/EISN/Shared%20Documents/Epidemiology%20season%20documents/Meetings%27%20reports/Slovenia%20report_2011.pdf. Accessed September 2012.

[5] Aguilera JF, Paget J, Manuguerra JC. Descriptive survey of influenza surveillance systems in Europe final report. (http://www.euroflu.org/documents/eiss_inventory_survey_dec_2000.pdf). Accessed September 2012.

[6] Aguilera JF, Paget WJ, Mosnier A et al. Heterogeneous case definitions used for the surveillance of influenza in Europe. Eur J Epidemiol 2003; 18:751–754.

[7] Aguilera JF. WHO. Protocol for the Evaluation of the Quality of Clinical Data within the European Influenza Surveillance Scheme (http://www.euroflu.org/documents/eiss_clinical_data_evaluation_protocol.pdf). Accessed September 2012.

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[9] Vega T, Lozano JE, Meerhoff T, Snacken R, Mott J, Ortiz de Lejarazu R, Nunes B. Influenza surveillance in Europe: establishing epidemic thresholds by the Moving Epidemic Method. Influenza Other Respi Viruses 2012; DOI:10.1111/j.1750- 2659.2012.00422.x.