Practical guidance for national influenza centres establishing or implementing neuraminidase inhibitor susceptibility surveillance

Updated 2018

World Health Organization

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Abbreviations and acronyms

AVST	antiviral susceptibility testing
CC	collaborating centre (WHO)
CDC	Centers for Disease Control and Prevention
GISAID	Global Initiative on Sharing All Influenza Data
GISRS	Global Influenza Surveillance and Response System
HRI	highly reduced inhibition
IC_{50}	half maximal inhibitory concentration
IRR	International Reagent Resource
MTA	materials transfer agreement
NA	neuraminidase
NAI	neuraminidase inhibitor
NI	neuraminidase inhibition
NIC	national influenza centre
PCR	polymerase chain reaction
RI	reduced inhibition
RT-PCR	reverse transcription-polymerase chain reaction
SARI	severe acute respiratory infection
SNP	single-nucleotide polymorphism
TESSy	The European Surveillance System
WHO	World Health Organization

Summary

Surveillance of influenza antiviral susceptibility has become more important as use of antivirals has increased, and it now plays an important role in influenza control procedures. Antiviral surveillance capability within Global Influenza Surveillance and Response System laboratories is required to ensure good coverage in each World Health Organization region. However, there is debate about the scale of testing required; in contrast to virus detection, there is no expectation that every laboratory should perform antiviral susceptibility testing (AVST). Some national influenza centres wish to implement antiviral surveillance, but are not fully aware of the laboratory requirements for such surveillance.

All influenza surveillance systems and effective control measures, whether national or international, depend on the consistent and successful implementation of key laboratory activities. The implementation of AVST in a laboratory depends on factors such as available expertise, financial resources and facilities; it also depends on overcoming any difficulties in acquiring or importing the necessary equipment and consumables, or in establishing equipment maintenance contracts.

This document discusses the practical considerations that must be assessed when deciding whether implementation of AVST within a laboratory is practical, the long-term costs of testing, and the requirements for testing in terms of resources (both equipment and reagents) and staff training.

A checklist given at the end of the document allows a simple self-assessment of whether a laboratory can establish and maintain AVST capability.

1. Surveillance systems and specimen selection

In surveillance systems and specimen selection, the first thing to note is that antiviral susceptibility testing (AVST) should be integrated into existing surveillance systems rather than being a stand-alone activity. Consequently, laboratories that intend to establish AVST need to consider the surveillance systems that are already in place. This will allow laboratories to ensure that they receive relevant specimens and complementary information (epidemiological and clinical) for analyses and upload of data to existing systems. When establishing AVST, it is crucial to set priorities for which specimens to test, as shown in Table 1, in order to implement a cost-effective strategy while simultaneously meeting surveillance requirements. National influenza centres (NICs) need to adopt the best strategy, based on their existing capacity, to fulfil their objectives and requirements, taking into account AVST of community, hospital and severe acute respiratory infection (SARI) specimens, and of specimens from specific groups or situations.

1.1 AVST of community specimens

The collection of specimens from patients presenting to health care systems is an essential routine component of national networks for influenza surveillance. This surveillance, based on randomly selected influenza virus positive samples, is of epidemiological importance because it makes it possible to determine:

- baseline antiviral susceptibility among circulating viruses; and
- the frequency of viruses with reduced inhibition (RI) or highly reduced inhibition (HRI), or those carrying amino acid substitutions associated with resistance or RI/HRI, which can be used to identify trends.

Specimens from the untreated community are the most important for determining changes in resistance or RI/HRI, because the number of viruses exhibiting resistance or RI/HRI can be put into context more easily than is the case with specimens from treated patients. Ideally, such specimens should come from a community sentinel surveillance scheme in which basic clinical information can be collected and patients can be followed up. If no such scheme is in place, non-sentinel community specimens should be tested. The number of specimens that should be tested will depend on the number of positive specimens received and the laboratory capacity, which may change from year to year. For comprehensive surveillance by any method, samples selected for testing should be distributed throughout the influenza season.

For phenotypic (half maximal inhibitory concentration – IC_{50}) testing, a minimum target of 40 viruses, covering all types and subtypes, is ideal. This will ensure that sufficient data are available for development of seasonal and subtype-specific criteria for identification of unusual viruses. For both genotypic and phenotypic testing, randomly selected specimens spanning the entire influenza season should be tested, based on the date of disease onset (if known) or the date of sample collection. If laboratory capacity allows, at least the first 10 viruses of each type and subtype should be tested, reducing to a reasonable proportion (10–20%) of virus isolates during the season peak. At the end of the season, when the number of isolates is below 10 per week, most isolates should be tested.

The data collected from AVST of community specimens are important from a public health perspective, because they provide information on whether viruses displaying RI/HRI can undergo sustained transmission in the community and retain the ability to cause disease. The data emerging can lead to public health actions, such as the periodic revision of guidelines (e.g. for antiviral treatment and chemoprophylaxis) and the issuing of alerts to scientific and clinical communities.

Table 1. Specimen sources important for antiviral susceptibility surveillance

Type of specimen	**Purpose**	**Necessity**	**Number and timing of specimens**
Sentinel specimens	• Determines a baseline of susceptibility in circulating viruses • Determines the frequency of viruses that are resistant or show RI/HRI; essential for informing national and international policy on neuraminidase inhibitor use	**Highly desirable**	Random selection based on laboratory capacity: • 40 minimum • selected throughout a season to include the first 10 of each (sub)type, followed by every fifth isolate throughout a season • majority when detections fall below 10 per week
Non-sentinel specimens			
Type of patient	**Patient characteristics**	**Necessity**	**Timing of specimens**
Immunocompromised patients (treated)	• Likelihood of prolonged virus shedding • Likelihood of high virus load	Where available	Pre- and post-treatment specimens from each patient, and ongoing specimens if the patient is found to be shedding virus over a prolonged period of time
Patients becoming influenza positive during or after receiving postexposure prophylaxis	Insufficient drug dose increases the likelihood of resistance emergence	Where available	Earliest and latest influenza positive specimens
Any treated patients, but especially those with prolonged therapy or shedding	Determines the frequency of resistant viruses emerging under treatment	Where available	Pre- and post-treatment; monitor for duration of virus shedding
Severe cases	Monitors for any changes in clinical impact or epidemiology associated with resistance	**Highly desirable**	Selected specimens over the duration of virus shedding
Fatal cases	Monitors for any changes in clinical impact or epidemiology associated with resistance	**Highly desirable**	Earliest and latest influenza positive specimens
Outbreaks (e.g. in care or nursing	Higher probability of close contact and localized	**Highly desirable**	Selected early, mid and late outbreak specimens