

41. SPECIFIC TERMS OF REFERENCE FOR THE NCR FOR DRUG-RESISTANCE AMONG DNA VIRUSES

AIMS

- Each National Reference Centre (NRC) must meet both the general and the specific terms of reference.
- In the specific terms of reference, the NRC tasks dedicated to each selected pathogen or group of pathogens are described.
- These aim to guarantee the knowledge, the know-how and the epidemiological surveillance expertise of each NRC.
- The task list is not exhaustive and can be modified in function of the requirements and the evolution of knowledge and techniques.
- In the event a NRC is unable to perform a specific task, this can be subcontracted to preserve the knowledge in the NRC. If this is the case, quality of the subcontracted task has to be proven and assured.
- Each list of specific terms of reference is divided into three parts: 1) a reminder of the specific missions, 2) a description of the tasks that the NRC must be able to do including the competencies and 3) a list of the tasks that will be asked in a particular context.
- The type of analysis indicated for each specific pathogen in each particular situation (diagnosis or confirmation, typing, sensitivity to antimicrobial substances, virulence...) is defined.
- The collaboration with national and international surveillance systems (e.g. ECDC) and when relevant with other reference centres (European Medicines Agency, food safety reference centres, veterinary reference centres, ...) is also a priority.

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SPECIFIC MISSIONS

1. To provide testing services for typing drug-resistant HSV-1, HSV-2, VZV, CMV and HHV-6 to currently approved antivirals that target herpesvirus DNA polymerases (i.e. acyclovir, penciclovir, ganciclovir and their oral prodrugs, foscavir and cidofovir) and the CMV terminase (i.e. letermovir).
2. To provide testing services to the investigational drugs maribavir (inhibitor of CMV UL97 protein kinase) and pretilivir (inhibitor of HSV helicase-primase complex).
3. To characterize herpesviruses drug-resistance phenotypically and/or genotypically.
4. To participate in national surveillance, transfer microbiological data (through e-health reporting) and contribute to the presentation and interpretation of the results in a public health approach.
5. To collaborate to European networks aiming to evaluate drug-resistance in herpesviruses.
6. To interact with epidemiologists and other NRC's with the aim to sustain/adapt the use of the various outputs (with regards to quality of care, recommendations for control/prevention, ...).

THE NRC MUST BE ABLE TO (LEVEL OF COMPETENCES)

1. Perform virus culture.
2. Carry out phenotyping (drug-susceptibility profile) of the isolated virus.
3. Accomplish genotyping of viral genes involved in drug-resistance: [UL97 (protein kinase) and UL54 (DNA polymerase) for HCMV; UL23 (thymidine kinase) and UL30 (DNA polymerase) for HSV, ORF36 (thymidine kinase) and ORF28 (DNA polymerase) for VZV and U69 (protein kinase) and U38 (DNA polymerase) for HHV-6].
4. Detect co-infection with different viral strains.
5. Monitor samples from different body compartments.
6. Complete longitudinal evaluation of emergence of drug-resistance.
7. Construct maps for all genes known to be responsible for drug-resistance with all the known mutations associated with either drug-resistance or with genetic polymorphism.
8. Detect new mutations associated with drug-resistance or genetic polymorphism.

TASKS THAT WILL BE ASKED IN A PARTICULAR CONTEXT

1. To contribute to the functioning of the interactive network with different national and international hospitals.
2. To analyze drug-resistance for other DNA viruses when requested, such as
 - Epstein-Barr virus and Kaposi's sarcoma-associated herpesvirus (KSHV) genotyping of the viral DNA polymerase.
 - adenoviruses phenotyping (drug-susceptibility profile) and/or genotyping after performing adenovirus typing.
 - BK virus (polyomavirus) genotyping of the viral Large T antigen.
3. To play a role in education and training of virologists and laboratory technicians in techniques of herpesvirus drug-resistance testing.
4. To participate in international networks of viral drug-resistance among DNA viruses.