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Antiviral Research 95 (2012) 167–171

Contents lists available at SciVerse ScienceDirect

Antiviral Research

journal homepage: www.elsevier.com/locate/antiviral

Review

The European Virus Archive: A new resource for virology research

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ARTICLE INFO

Article history:
Received 2 April 2012
Revised 8 May 2012
Accepted 9 May 2012
Available online 22 May 2012

Keywords:
Virus
Archive
Access
Reagents
Kits
Diagnosis
Storage
Freeze-drying

ABSTRACT

The European Virus Archive (EVA) was conceived as a direct response to the need for a coordinated and readily accessible collection of viruses that could be made available to academia, public health organisations and industry, initially within Europe, but ultimately throughout the world. Although scientists worldwide have accumulated virus collections since the early twentieth century, the quality of the collections and the viruses collected may vary according to the personal interests and agenda of the scientists. Moreover, when laboratories are re-organised or closed, collections are no longer maintained and gradually cease to exist. The tragedy of 9/11 and other disruptive activities have also meant that some previously available biological reagents are no longer openly exchanged between countries. In 2008, funding under the FP7–EU infrastructure programme enabled the initiation of the EVA. Within three years, it has developed from a consortium of nine European laboratories to encompass associated partners in Africa, Russia, China, Turkey, Germany and Italy. There is every reason to believe that EVA will continue to expand and ultimately exist as a globally networked, quality-controlled non-profit archive for the benefit of science. Organizations or individuals who would like to be considered as contributors are invited to contact the EVA coordinator, Jean–Louis Romette, at jean-louis.romette@univmed.fr.

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0166-3542/$ - see front matter © 2012 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.antiviral.2012.05.005

1. Introduction: the European Virus Archive

The European Virus Archive (EVA) was conceived as a direct response to the need for a coordinated and readily accessible collection of viruses that could be made available to academia, public health organisations and industry, initially within Europe, but ultimately throughout the world. In 2008, funding under the FP7–EU Infrastructure programme enabled the initiation of the EVA. Within three years, it has developed from a consortium of nine European laboratories to encompass associated partners in Africa, Russia, China, Turkey, Germany and Italy. There is every reason to believe that EVA will continue to expand and ultimately exist as a globally networked, quality-controlled non-profit archive for the benefit of science. In this paper, we provide a summary of the structure, management and goals of the EVA, to inform researchers of the wealth of resources it can provide and to help them gain access to those resources.

2. History of virus archives

Laboratory isolation and characterisation of viral pathogens, such as poliovirus, foot and mouth disease virus, yellow fever virus and others, began at the turn of the twentieth century. This represented a pioneering era in the development of medical and veterinary virology. Within years of these first experiments, virological diagnostic and research centres were established worldwide to investigate a large range of unidentified aetiologic agents that had not been cultured under laboratory conditions. Large numbers of mammalian viruses have now been isolated, although current evidence suggests that this is only the tip of the iceberg as more and more new viruses are being discovered, almost daily, using rapidly developing molecular technologies. However, the isolation, identification, characterisation and preservation of these virus collections have inevitably generated new challenges.

Many of the viruses are stored quite arbitrarily in collections that are often lost when the virologist responsible for their identification and storage retires or when a laboratory closes down or is reorganised. Other collections are unavailable to the wider virology community because scientists are unwilling to distribute their viral isolates. Moreover, governments have introduced new laws to secure their borders against terrorists. Thus, in many circumstances viruses are no longer allowed to be moved across the borders; the 9/11 tragedy is a prime example, having contributed to increased restrictions. For European countries, the US is no longer a reliable source, for provision of viruses for research, diagnosis, industry or teaching purposes. Moreover, laboratories in Russia, China, India and south East Asia, hold their own collections many of which, to date, have been relatively inaccessible to European laboratories.

Viruses in most families have been identified on the African continent and laboratories in Africa have made their collections easily accessible to researchers in Europe and the Americas. Sadly, virus collections are virtually non-existent with the exception of a few countries such as South Africa and Kenya. Some research laboratories have accumulated collections of viruses that are primarily dependent on the particular speciality of the laboratory. For example, the American type culture collection (ATCC) and the centre for disease control and prevention (CDC) (USA) maintain diverse collections of mammalian viral pathogens (including Biosafety level 4 agents). Laboratories in Russia, China, India, south East Asia, South Africa, Australia and New Zealand, hold collections that have been isolated in their countries. Relatively large collections of arboviruses are currently held in Texas, France, the Czech Republic, Slovakia and also in Scandinavia. A national collection of pathogenic viruses (NCPV–ECACC) has been prepared in the United Kingdom (UK), at the Health Protection Agency and European collections of specified animal pathogens, particularly rabies and influenza viruses are maintained in the UK (Animal Health and Veterinary Laboratories Agency) and in France at the Pasteur Institute. Biosafety level 4 (BSL4) viruses such as Ebola, Nipah etc., are maintained in specialised facilities in France, Germany, Russia, the US and the UK. Many other assorted viruses of medical and general veterinary importance (coronaviruses, herpesviruses, retroviruses, adenoviruses, enteroviruses, etc.) are held in laboratories around the world.

3. The EVA: a new, multilateral approach to archiving

As the above survey indicates, the process of coordinating virus standardisation, characterisation, preservation and distribution, has inevitably been relatively arbitrary and largely dependent on the particular speciality of each laboratory. In summary, other than EVA, we are unaware of any centre in the world which as a non-profit making organisation, systematically coordinates and globally distributes viruses and associated reagents from individual virus collections to research and/or diagnostic laboratories, teaching centres, industries involved in the production of diagnostic reagents, pharmaceuticals, and vaccines, solely for the benefit of science, in a safe and controlled manner. It would be virtually impossible to establish a single laboratory to maintain supplies of all recognised mammalian viruses. EVA overcame this problem using the web to centralise accessibility to quality controlled, validated viruses held in laboratories worldwide. The concept was simple but because virologists are naturally protective of their own collections, its success required a paradigm shift in the mindset of the partners or associated partners in the individual laboratories.

The *7th Framework programme of the European Union (EU)* placed a call for funding applications under the heading "CAPACITY", with sub-headings one of which was "Research Infrastructures". Accordingly, the concept of the European Virus Archive was created and a funding proposal was submitted in response to the EU call. In preparing the proposal it was emphasised that it would be virtually impossible to generate a wide ranging viral archive in a single laboratory complex. Thus, although many high calibre virus laboratories operate in Europe, it was decided to re-

Table 1
European partner laboratories that form the core of EVA.

Name of participating organisation	Country
Institut de Recherche pour le Développement (IRD)	France
Animal Health and Veterinary Laboratories Agency (AHVLA)	UK
Bernhard-Nocht-Institut für Tropenmedizin (BNI)	Germany
Universitaetsklinikum Bonn (UKB)	Germany
Health Protection Agency (HPA)	UK
Université de Genève (UNIGE)	Switzerland
Univerza v Ljubljani (UL)	Slovenia
Institute of Virology, Slovak Academy of Sciences (IVSAS)	Slovakia
Université de la Méditerranée (UNIVMED)	France

tain the "virology club tradition" by developing the principle of an integrated infrastructure via consortia, operating through validated networks. As far as we are aware, this concept had not previously been encompassed by virologists in the context of producing and providing access to viruses.

EVA was therefore conceived to fill the gaps in accessing viruses through identification of appropriate European laboratories. It was agreed that by integrating their collections or resources and devising appropriate validated protocols and effective dissemination procedures, the partner laboratories would be able to work to identical high standards in producing and supplying authenticated viruses to the scientific community both within and outside Europe. EVA is unique. It has been conceived to generate the largest collection of mammalian viruses in the world and move beyond the current state-of-the-art to provide an increasingly valuable resource and service to the global scientific community, to government health departments, to higher education institutes, to industry and, through information systems, to the general public.

4. EVA organizational structure

In the first instance, only laboratories within the EU were directly eligible for EVA funding although the concept of non-funded associated laboratories outside the EU was acceptable. Consequently, nine high calibre European partner laboratories agreed to become the primary members of the EVA consortium. These are listed in Table 1.

EVA is founded on the principle that members and associate members of the consortium retain ownership of the viruses that they disseminate via the EVA infrastructure. The virologist or institution that supplies the viruses to the customer retains the ownership and enters into agreements with the customer via material transfer agreements (MTAs). All orders for viruses and associated reagents (cell cultures, recombinant proteins, RNA, plasmids, monoclonal antibodies. . ..), are placed via the EVA website www.european-virus-archive.com, which is managed centrally in Marseille (partner#1, IRD).

During the early stages of the existence of EVA, emphasis was placed on establishing the collections of viruses and associated reagents and ensuring that quality control was managed centrally. This ensured that all laboratories complied with identical standards. A scientific advisory board consisting of experts in virology, immunology and molecular biology, was established:

- Professor Ernest Gould, (President of the board) former Director of the Institute of Virology (subsequently known as the Centre for Ecology and Hydrology CEH, Oxford, UK). Prof. Gould has been a virologist for nearly 40 years and has worked on a wide range of viruses.
- Professor Rolf Zinkernagel, Nobel laureate in Physiology or Medicine 1996 (University of Zurich, Switzerland). Prof. Zinkernagel is world renowned for his studies on how the immune system recognises virus-infected cells.
- Professor Robert Tesh (University of Texas, Medical Branch, USA) director of the World Reference Center for Emerging Viruses and Arboviruses.
- Doctor Jan terMeulen (Merck USA) has broad experience in virology and immunology. He is currently the Executive Director for Vaccines research and development of Merck, Princetown, USA.
- Professor Richard Elliott (School of Biology, University of St. Andrews, UK). For many years, Prof. Elliott has focused his research on molecular biological aspects of bunyaviruses, becoming a world-renowned expert.
- Dr. Peter Daniels (Australian Animal Health Laboratory - AAHL). Through his work at AAHL and involvement with epidemic outbreaks in south-east Asia, Dr. Daniels has gained an immense amount of experience in diagnosis, surveillance and control of a broad range of virus diseases that, in addition to important arboviruses, include menangle virus, avian influenza virus and Nipah virus.
- Dr. Valery Loktev (Institute of Molecular Biology –VECTOR, Novosibirsk, Russia). Dr. Loktev specialises in human encephalitic and haemorrhagic disease due to tick-borne encephalitis virus and other related viruses including West Nile virus.

Once established and operating satisfactorily, EVA management began the process of contacting laboratories outside Europe, organising meetings and conferences with these laboratories and subsequently inviting them to become associate partners within EVA. Currently associate partnerships have been negotiated and agreed in South Africa, Russia, China, Turkey, Germany and Italy (Table 2). The initiation and early progress of EVA is already a tremendous achievement and subject to its continued success and expansion, the hope is that EVA will become a global network of laboratories contributing to the sharing of resources and promoting advances in virology.

5. EVA resources and management

5.1. Viruses available through the EVA catalogue

The list of quality controlled viruses is continuously expanding. However, in addition to viruses, some EVA partners may also be able to supply a range of clinical materials containing human or animal viruses. Relevant information can be requested by entering an enquiry on the website. The list currently includes viruses in the families, *Picornaviridae, Rhabdoviridae, Bunyaviridae, Paramyxoviridae, Orthomyxoviridae, Flaviviridae, Togaviridae, Herpesviridae, Reoviridae, Filoviridae*. In addition, a range of arthropod tissue culture cell lines, monoclonal antibodies, recombinant protein expression systems, purified viral RNA, specialised kits for diagnosis and custom-made proteins, can also be obtained through the EVA website.

5.2. Quality control, safety standards and biosecurity

The laboratories of each partner or associate partner comply with quality control and safety standards, as recommended by internal experts. In addition, all partner laboratories are inspected and comply with the safety and biosecurity standards according to the individual regulations of the country in which they work. "All potentially hazardous biological material is packaged and supplied to the customer in containers that meet the appropriate standards of the country from which the samples are dispatched. The goods

Table 2
Currently agreed associate partners in EVA.

Dr. Claude Sabeta	Onderstepoort Veterinary Institute, Praetoria, South Africa
Prof. Mikhail Eropkin	Research Institute of Influenza, St. Petersburg, Russia
Dr. Alexander Lukashev	Chumakov Institute of Poliomyelitis and Viral Encephalitides, Moscow, Russia
Prof. Andrei Kozlov	Biomedical Centre, St. Petersburg, Russia
Prof. Vitali Zverev	Mechnikov Research Institute, Moscow, Russia
Prof. Dmitri Lvov	Ivanovsky Institute of Virology, Moscow, Russia
Dr. German Shipulin	Center for Molecular Diagnostics, Moscow, Russia
Prof. Anatoly Zhebrun	St. Petersburg Pasteur Institute, St. Petersburg, Russia
Prof. Matthias Niedrig	Robert Koch Institut, Berlin, Germany
Prof. Giuseppe Ippolito	UOC, Istituto Nazionale Malattie Infettive, Roma, Italia
Prof. George Gao Fu	Laboratory of Pathogenic Microbiology, Chinese Academy of Science, Beijing, China
Prof. Guo-Dong Liang	Dep't. of Viral Encephalitis and Arbovirus, China–CDC, Beijing, China
Prof. Ergunay Koray	Hacettepe University, Faculty of Science, Biology Department, Ecology Division, ESRL Laboratories, Ankara–Turkey

are transported via express mail using companies that comply with international standards. All packaging and dispatch procedures follow the guidelines prepared by experts in the Animal Health and Veterinary Laboratories Agency, UK.

As an additional security measure, customers must provide details of their authenticity and satisfy EVA personnel that they are legitimate users by describing the nature of the proposed work and details of the available biocontainment facilities, scientific expertise and references to relevant published science.

5.3. Management and dissemination of information

A team of scientists and administrators is dedicated to the management of EVA to ensure continuity and to maximise the efficiency of EVA. Currently, only one laboratory in Europe (the National Collection of Pathogenic Viruses – NCPV – incorporated into ECACC) has developed a web-based catalogue for the distribution of a limited number of mammalian viruses. This laboratory is a partner in EVA and additionally provides this knowledge and experience of developing their latest web-based catalogue. Whilst the individual laboratories within EVA operate through the web-based catalogue, they supply to the end-user only the viruses and products that are held in their collections. The EVA website is conceived as a database-driven site, by achieving complete separation between the design and the presented content. It is based on the publishing system SPIP (http://www.spip.net/en), structured with PHP and MySQL.

The EVA website consists of two major areas, the first is accessible to the general public, and includes the entry point to request viruses and associated reagents from EVA. The second is accessible only to EVA partners and associated partners. The area of the website accessible to the general public displays a wide range of information from the project description to non-private scientific information. This includes events related to the project, educational material including videos and other documents relating to virology in the context of taxonomy, pathogenesis, epidemiology, diagnosis and control. It also displays an up-to-date list of the publications related to the project. The website is the main tool for the dissemination of EVA products. A specific portal was conceived as an e-shop and constitutes a single entry point to the EVA bioresource. This EVA Portal is a user friendly interface to a part of the EVA database, through which a customer can easily place any enquiry.

If the customer is employed in an EU-member state or in an EU-associated state he/she may be entitled to free access to the virus or associated reagent(s). An international panel, consisting of independent experts, reviews the request for free access and subject to approval the customer will receive the item without charge other than covering the cost of transportation. In the case of a charge being required to supply the virus or reagent, EVA only recovers the cost of production and transportation to the customer.

The restricted area of the website requires the users' identification to obtain access. The website contains two of these restricted areas. (i) The "Consortium" area of the website which is only accessible to project members. It contains private information about work packages (WP) and tasks, derived products protocols, management information, training materials and other documents/information provided by the corresponding dissemination section. This area of the website also hosts interfaces that provide access to the EVA-database (DB) content. (ii) The "associate members" area of the website is dedicated to an increasing partnership as new collections are added to the EVA consortium. This area therefore provides associate members with access to data not disclosed in the general public area and enables associate partners to share information with the original consortium members by adding content to the EVA–DB. Security for restricted access areas of the EVA website (dealing with information that cannot be disclosed) is ensured using the SSL protocol for encryption.

6. How will EVA contribute to the control of viral diseases?

The EVA infrastructure provides wide-ranging and efficient access to virus collections held in laboratories worldwide, with the potential for access to recently isolated viruses from clinical, veterinary and field samples. The collection will continually expand, as the number of contributing laboratories increases. EVA will provide participants with access to materials, including:

- freeze-dried viruses for long-term storage;
- reagents and kits, including primer sequences and appropriate protocols for virus identification;
- standardised diagnostic kits and recombinant proteins representing genes of the viruses, or hyperimmune antisera with defined specificities;
- custom-prepared kits, proteins and antibodies;
- high quality associated research laboratories;
- viruses validated by sequencing, including the "rescue" and characterisation of archival material.

EVA also potentially provides access to isolates of specific interest, following analysis of sequence databases through relevant web-links, which will be established via the EVA catalogue. This concept will enable laboratories in developing countries to contribute to the expanding pool of quality-controlled viruses and reagents. Our approach will make it possible for contributors, including those from developing countries, to accommodate local ethical priorities through retention of ownership of their viruses and reagents. EVA will therefore serve science, environmental and public health authorities, and will also meet the needs of the

pharmaceutical industry, in developing new technologies for disease control.

EVA also provides participants with access to information, including:

- protocols for virus inactivation;
- standardised protocols for virus production, assessment, storage and distribution;
- materials for diagnosis, teaching and training purposes;
- workshops, international conferences, educational and training courses;

The combined experience and knowledge of the partners is available to assist participants in the EVA programme, providing opportunities for closer interactions between scientists from many related disciplines.

7. Current status and future of EVA

EVA is now in the third year of its existence under Framework Programme 7. The ultimate objective of EVA is to make it a permanent archive that can provide access to viruses and reagents globally. This will be achieved through extension of the funding arrangements and also through expansion of the range of contributors to the collection.

The concept of EVA is unique. As far as we are aware, there is no equivalent viral archive. Nor does any other collection provide the accessibility, reagent backup, sequence data, provenance, quality control, and capacity to inform, through the web. The reputations, high quality, experience and knowledge of the EVA partners, combined with the integration of the EU Community infrastructure, and collaborative projects and informational programmes developed in EVA, will provide end-users with opportunities to approach new fields of research in structural viral genomics, evolutionary biology, control of infectious diseases, antiviral drugs design, fundamental research, public and environmental health, pathogenesis, immunology and a wide variety of associated disciplines. Subsequently, subject to continuation of funding, EVA aims to extend this seed pool to encompass all areas of virology (i.e. beyond mammalian virology) and all geographic regions of the world. This will be achieved firstly through expansion within the European Community and then integration of specialist laboratories, in the Americas, Russia, Asia, China, Australia and Africa. EVA will investigate additional opportunities to improve the scope of its original concept for the benefit of science. These will include, exploring the possibility of forming partnerships and alliances with other Community Programmes including GOARN/WHO, E–CDC and C–CDC. With the provision that funding will be required, there is no obvious limit to the range of possibilities that might be explored.

Whilst this is an ambitious programme, it will develop incrementally, continuously utilising the individual networks of the partners and members of the SAB to enable the expansion and quality control programmes. It would be wrong to suggest that this programme of expansion will be straightforward. For example, perpetuation of EVA firstly requires a continuous and increasingly large funding stream to meet the almost restrictive costs of laboratory development and upkeep in the face of newly emerging highly pathogenic viruses. To a limited extent such obstacles are mediated by the concept of having many partner laboratories in EVA, each of which operates independently. Nevertheless, as safety, biosecurity and quality control standards continue to be raised, greater efforts will be required to maintain the archive. However, given the will to continue in developing EVA, its ultimate success will generate a unique collection that benefits all areas of biology, medicine and associated industries.

We believe EVA has made outstanding progress during its first three years of existence. However, it is still in its relative infancy. The concept of a single, centralised web-based catalogue that links laboratories from all over the world is simple but robust. The most common difficulty encountered in maintaining a service to the scientific community is to generate a continuous funding source. By spreading itself so widely and using well-established laboratories, with well-organised infrastructures, that in many cases provide backup for other partner laboratories, the EVA should generate long-term stability and sustainability.

Acknowledgements

We wish to thank the following scientists for their expertise and contributions during the successful establishment and development of EVA: P. Lieutaud, N. Ghandour, R. Charrel, B. Canard, D.L. Horton, E. Wise, M. Bardsley, J.F. Drexler, S. Oelschlaeger, D. Lewis, C. Rowe, M. Lickova, M. Lahova, S. Havlikova, M. Korva, A. Saksida.