



The European Virus Archive goes global: A growing resource for research

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ABSTRACT

The European Virus Archive (EVA) was created in 2008 with funding from the FP7-EU Infrastructure Programme, in 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. Within three years, it developed from a consortium of nine European laboratories to encompass associated partners in Africa, Russia, China, Turkey, Germany and Italy. In 2014, the H2020 Research and Innovation Framework Programme (INFRA4 projects) provided support for the transformation of the EVA from a European to a global organization (EVAg). The EVAg now operates as a non-profit consortium, with 26 partners and 20 associated partners from 21 EU and non-EU countries. In this paper, we outline the structure, management and goals of the EVAg, to bring to the attention of researchers the wealth of products it can provide and to illustrate how end-users can gain access to these resources. Organisations or individuals who would like to be considered as contributors are invited to contact the EVAg coordinator, Jean-Louis Romette, at jean-louis.romette@univmed.fr.

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1. Introduction

The European Virus Archive (EVA) was created in 2008 with funding from the FP7-EU Infrastructure Programme, in 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 (Gould et al., 2012). Within three years, it developed from a consortium of nine European laboratories to encompass associated partners in Africa, Russia, China, Turkey, Germany and Italy. Following the H2020, 2014 call for Research and Innovation Framework Programme (INFRA projects) the concept of developing the EVA into a global organization was a natural progression and the project was funded for a four-year period. In April 2015, the EVAg started to operate as a non-profit consortium including 26 partners and 20 associated partners from 21 EU and non-EU countries. Based on excellent progress during the first two operational years, we have every reason to believe that the consortium will continue to expand and will ultimately constitute the world's largest virus collection. In this paper, we outline the structure, management and goals of the EVAg, to bring to the attention of researchers the wealth of products it can provide and to illustrate how end-users can gain access to these resources.

2. History of virus archives

Laboratory isolation and characterisation of viral pathogens, such as vaccinia virus, 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. Over the years, diagnostic and research centres were established worldwide to investigate viruses causing a wide range of diseases including those that had hitherto escaped all attempts to be identified and cultured under laboratory conditions. In the 21st century, ever-growing numbers of mammalian viruses continue to be isolated. They may represent only the tip of the iceberg, as more viruses are being discovered and reported using rapidly developing molecular technologies.

As a result of these advances, the isolation, identification, characterisation and preservation of growing virus collections has inevitably generated new challenges. Many of the known viruses are in collections that may be lost or discarded when the virologist in charge retires or when a laboratory closes or is reorganized. Other collections may not be available to the wider virology community, because scientists are not always willing or in a position to share their viral isolates. They may lack the infrastructure, time (manpower), facilities and experience to characterize and present their collection in an accessible catalogue and further be able to ship their collected strains to foreign countries due to the restraints imposed by increasingly complex transportation regulations. Furthermore, many governments have introduced additional security measures that specifically regulate the transfer and/or exchange, between countries, of high-risk-group pathogens that may attract the interest of terrorist organisations. Additionally, laboratories in Russia, China, India, Southeast Asia and South America hold their own virus collections, many of which, to date, have been relatively inaccessible to European laboratories. Viruses from many taxonomic families have also been identified on the African continent and some well-developed laboratories in Africa have made their collections readily accessible to researchers in Europe and the Americas. Currently, however, except for a few countries, including Senegal, South Africa and Kenya, authenticated virus collections from other regions of Africa are virtually non-existent.

One objective of the EVAg therefore has been to establish trust among these widely disparate institutes and to associate the scientists in these countries with partners in the consortium under carefully monitored conditions that protect these developing laboratories, to the mutual benefit of everyone. The current project aims at the development of virus collections in low-income countries where, in some cases,

there has been an understandable reluctance to exchange viruses for fear of losing their resource to institutes from more highly developed countries. The EVAg infrastructure provides assured access to modern capacities, thereby assisting these institutes to train their staff in developing their own resources and expanding and maintaining these capacities locally. End-user requests for viruses and reagents from these developing laboratories will be entirely managed from within, but supported by the quality management and distribution systems of the consortium. In common with all other members of the consortium, these developing laboratories will automatically retain full ownership of their collections.

Elsewhere, research laboratories often accumulate collections of viruses that are primarily dependent on the speciality of the laboratory scientists. For example, the American Type Culture Collection (ATCC) and the US Centres for Disease Control and Prevention (CDC) maintain large collections of mammalian viral pathogens, including Risk Group 4 (RG4) agents. Laboratories in Russia, China, India, Southeast Asia, South Africa, Australia and New Zealand hold collections that have been isolated specifically in their countries. Relatively large collections of arboviruses are currently held in the USA (Galveston National Laboratory, Texas), France, the Czech Republic, Slovakia and also in some countries of Scandinavia. European collections of specified animal pathogens, particularly lyssaviruses, pestiviruses, arboviruses and influenza viruses are maintained at the Animal and Plant Health Agency and at The Pirbright Institute in the United Kingdom; in Italy at the Istituto Zooprofilattico Sperimentale delle Venezie (IZSVe) hosting the World Organization for Animal Health/Food and Agriculture Organization (OIE/FAO) and EU reference laboratory for avian influenza; and in France at the Institut Pasteur. RG4 viruses such as Ebola and Nipah are maintained in specialised facilities in France, Germany, Russia, the USA, China, South Africa and the UK. Diverse viruses of medical or veterinary importance (coronaviruses, herpesviruses, retroviruses, adenoviruses, enteroviruses, etc.) are held in laboratories around the world. As the EVAg continues to develop and to expand its boundaries, access to a greater proportion of these viruses will be enabled where possible.

Recently, in meeting the challenges of emerging viruses, the consortium has voluntarily oriented a part of its activities to the support of the World Health Organization (WHO) during emerging health crises by dedicating a new work-package entitled “Response to emergence”. Moreover, the EVAg is currently an associated partner of the Global Outbreak Alert and Response Network (GOARN).

3. The EVAg: a multilateral approach to archiving

Current processes of coordinating virus standardisation, characterisation, preservation and distribution are inevitably relatively arbitrary, and are largely dependent on the speciality of each laboratory. In fact, besides the EVAg, we are unaware of any non-profit organization that is concerned with facilitating reliable access globally to viruses and associated reagents from individual virus collections for research and/or diagnostic laboratories, teaching centres or industries involved in the production of diagnostic reagents, pharmaceuticals and vaccines solely for the benefit of science, in a safe and carefully regulated manner. It would be virtually impossible to establish a single laboratory to maintain supplies of all recognised pathogenic mammalian viruses. Based on the knowledge and experience gained from the former EVA project, we have addressed these problems by using web-based tools to centralise access to quality-controlled, standardised preparations of viruses held in laboratories worldwide. The underlying concept is simple, but because virologists are naturally protective of their collections, its success has required a paradigm shift in the mind-set of the partners or associated partners in the individual laboratories.

The H2020-INFRAIA-2014-2015 Framework programme of the European Union (EU) placed a call for funding applications under the heading “Research and Innovation Action,” with sub-headings, one of

which was “Research Infrastructures.” Accordingly, the concept of the EVAg was created and a funding proposal was submitted. In preparing the proposal, it was emphasised that it would be virtually impossible to generate a wide-ranging virus archive in a single laboratory complex. Thus, although many high-calibre virology laboratories operate in Europe, it was decided to retain the “virology club tradition” by developing the principle of an integrated international 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.

The EVAg was therefore conceived to fill the gaps in accessing viruses through identification of qualified international laboratories that could become partners of the consortium. 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 achieve common high standards in producing and supplying authenticated viruses to the scientific community,

both within and outside Europe. The EVAg is unique. It was conceived to move beyond the current state of the art and provide access to the largest collection of mammalian viruses and associated reagents in the world to the global scientific community, to government health and environmental departments, to higher education institutes and to industry, through appropriate information systems.

4. The EVAg organizational structure

The new approach was, in the first instance, to integrate non-EU partners as beneficiaries of the project. This was possible because the rule of reciprocal benefit was agreed: the non-EU partner provision activity of material to an EU entity (research institute, health organization, animal health-care structure, etc.) was eligible for financial compensation from the consortium EU budget. Consequently, 26 high-calibre European and non-European partner laboratories agreed to become the primary members of the EVAg consortium. These are listed in

Table 1

Partner laboratories that form the core of the EVAg, listed in chronological order of their integration into the project. Both medical and veterinarian institutes are included to cover viral zoonotic diseases. It also illustrates the wide geographic coverage already attained and demonstrates that BSL4 laboratories are major contributors to this consortium. The choice of institutes also reflects the specific available skills and know-how of scientists in institutes closely associated with the most well-known contemporary emerging viruses. We have also begun to integrate network organisations such as the Global Approach to Biological Research, Infectious diseases and Epidemics in Low-income countries (GABRIEL) Network, of the Fondation Merieux and the International Pasteur Institutes. Future plans include expansion of partnerships to countries not currently represented, such as Malaysia, Vietnam, Cambodia, Indonesia, South America, and additional African countries.

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Table 1.

In addition, 16 associate partners who share the same interest in the dissemination of viruses and reagents, but are not beneficiaries of the EU grant, have now been included (see Table 2). This association was formalized by the signature of a Memorandum of Understanding. The archive is founded on the principle that members and associate members of the consortium retain ownership of the viruses that they disseminate via the centralised distribution centre. 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, DNA, recombinant viruses, plasmids, monoclonal antibodies), are placed via the website <https://www.european-virus-archive.com/> which is managed centrally in Marseille by the Management team (partner#1, Aix-Marseille University).

During the early stages of the existence of the original 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. This principle has been further developed in the project. A manager was appointed to head up a Management Quality Committee with the responsibility of establishing and maintaining appropriate standards through close monitoring of procedures, protocols and record maintenance. To ensure uniformity throughout the consortium, the quality managers representing each partner form the body of the committee.

Previously, non-EU participants were given the status of associate partners, i.e. they were associated with the consortium, but were not full members. The objective was to evaluate the feasibility of this approach concerning both the collaborative exchanges related to development of a common infrastructure and the operational effectiveness of resource distribution. From the point of view of scientific collaboration, the process was established rapidly and functioned efficiently. However, standardisation of the procedure for the distribution of materials to end-users proved to be challenging, and it is still being developed and improved within the current consortium. The reason for this slow progress is almost entirely due to the complexity of national regulations. Whilst the European Regulations retain the principle of being national and are enforced primarily to control the circulation of pathogens, they have been developed to maintain uniformity throughout the EU countries. Thus, the administrative pathway to obtaining authorisation for an exchange of resources between, for

example, France and Germany or the Netherlands and Italy are very similar and are principally based on agreements provided by the National Biosafety Agencies. In contrast, the process of exchanging resources between the EU and Russia or between the EU and the USA involves many more constraints: the intervention of different administrations in processing authorisation for delivery of hazardous goods including, biosafety agencies, customs administration, commerce and trade administration, ministry of health, etc. (Also, the law in Russia does not permit the import or export of pathogens.) Nevertheless, our expertise in overcoming these hurdles is exemplified by the report of studies on the RG4 virus Crimean-Congo haemorrhagic fever virus in which the virus was supplied by a European partner to an end-user in the USA (Haddock et al., 2018). Not surprisingly, when Zika virus emerged in South America and was found to be responsible for microcephaly, we received numerous requests for Zika virus, and many papers have been published with recognition of the EVAg as the source of virus. Five examples encompassing, i) simultaneous transmission with chikungunya virus, ii) diagnosis, iii) signal processing pathways, iv) pathogenesis in relation to foetal infections and v) virus structure, are cited here (Goertz et al., 2017; Chan et al., 2017; Zhang et al., 2016; Miner et al., 2016; Sirohi et al., 2016).

These anticipated problems of transporting pathogenic viruses between countries, particularly outside Europe, were considered during the preparation of the project. Each potential barrier to efficient exchanges between different countries was extensively discussed and product dissemination objectives for each non-EU partner were defined depending on their specific status.

Once established and operating satisfactorily, the management team continued the process of contacting high-calibre laboratories outside Europe, organising meetings and conferences with these laboratories and subsequently inviting them to become associate partners. Currently associate partnerships have been negotiated and agreed with laboratories in Africa, Russia, China, Turkey, Australia, Japan, Germany, Italy, Hungary, South Korea, South East Asia and South America (Table 2). The initiation and early progress of the EVAg are already tremendous achievements, and subject to its continued success and expansion, it is anticipated that it will become the largest global network of laboratories contributing to the sharing of resources and promoting advances in virology.

Table 2

Currently agreed Associate Partners in the EVAg. The integration of institutes that share the same interest in research and in the provision of high quality products to the scientific community is made through an association formalized by the signature of a Memorandum of Understanding. The choice of the Associate Partners has been established to fill gaps or to extend the list of viruses currently offered in the catalogue, and to have EVAg present in geographical areas concerned by emerging virus outbreaks.

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|---|------------|---|
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5. Resources, management and access for end-users

Dissemination of resources including know-how and material to the scientific community is one of the major deliverable of the project. It has been addressed by the creation of web-based catalogue accessible on the EVAg portal. Quality of the offer is a key factor to differentiate EVAg from the other infrastructures proposing similar products to the end-user. The gold standard products listed on the catalogue have been clearly at the origin of the fast growing dissemination activity of the consortium and of its robust reputation as reliable provider of key components for the detection of emerging viruses acting under the umbrella of international health organisations.

5.1. Viruses and reagents available through the EVAg catalogue

The EVAg 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 and will provide participants with access to materials and capacities, including:

- freeze-dried viruses for long-term storage;
- viruses validated by sequencing, including the “rescue” and characterisation of archived material;
- 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 accessible to perform experiments and theoretical and practical training.

Relevant information can be obtained by placing an enquiry on the website (www.european-virus-archive.com/evag-portal). At the time of writing the catalogue shows more than 2000 products consisting of viruses and associated reagents. The list which is constantly increasing includes human, animal, insect, fish and plant viruses of medical, veterinary, academic, industrial and economic importance. 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-prepared proteins, can also be obtained through the website.

5.2. Quality control, safety standards and bio security

The approach to Quality Management is directed by the project's own Quality Standard, based upon Organization for Economic Cooperation and Development (OECD) guidelines, and critically focusses on the acquisition, characterisation and storage of virus products. Each partner institute seeks to comply with this way of working to harmonise laboratory processes across the consortium. The Quality Manager conducts “Best Practice” audits to quantify improvement progress. All facilities are inspected and regulated by their own national bio safety authorities, and employ staff trained in procedures compliant with the requirements of the International Air Transport Association (IATA) for the safe dispatch of potentially hazardous materials.

Trans-national access (TNA) ensures free of charge access to European research infrastructures and the costs of the research, products and associated activities. This opportunity is open to all European researchers and to some extent to researchers from non-EU countries. TNA dispatches include regulatory documentation such as import/export permits, and a certificate of analysis (CoA) provided by the supplying partner.

The EVAg project has established a grading system that defines virus

product quality ranked from 1 to 5, in which Grade 5 is the basic level, described as partially sequenced to confirm identity; not checked for mycoplasma contamination; unknown infectivity; and stored frozen. The “gold standard” is a fully sequenced virus, mycoplasma-free, with defined infectivity and lyophilised for long-term storage. Derived products such as proteins, nucleic acids or antigens are also prepared using standardised protocols and checked for quality before storage or dispatch.

Security at the consortium institutes is maintained using CCTV, PIN-coded passes and at remote sites, 24-h manned security/vehicle identification. Entry into bio containment laboratories is strictly controlled.

Supply of products to the applicants operates via the TNA approach defined above, whereby research groups apply through the web portal by submission of a completed request form. A successful application must be justified by an explanation of scientific objectives, techniques to be utilised/developed, list of named researchers, list of relevant publications and confirmation that appropriate expertise and facilities to handle the virus are in place. A review of these criteria is carried out by the project quality manager and a selection panel that includes external experts.

5.3. Management and dissemination of information

A team of scientists and administrators is dedicated to the management of the EVAg, to ensure continuity and to maximize efficiency. Whilst the individual laboratories operate through the web-based catalogue, they supply to the end-user only the viruses and products that are held in their collections. The website is the main communication tool with which to inform the end-user and to disseminate the products through the dedicated portal. The portal is conceived as a user-friendly marketplace that lists the viruses and associated reagents of each partner. This web-based catalogue constitutes a single entry point to the archived viruses and reagents. It provides access for end-users to place any enquiry about products of interest through a commonly used e-shop format.

Any end-user could be entitled to free access to the virus or associated reagent(s). The provider of the requested item(s) receives financial compensation from the EU budget. EU support for free-of-charge access provided to the end-user has as its main objective to facilitate access of the scientific community to high quality resources. However, this is conditional on the excellence of the project which the end-user aims to develop using the resource. 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, the EVAg only recovers the cost of production and transportation to the customer. Free-of-charge access to end-users employed outside EU-member or EU-associate states is limited to 20% of the total accesses provided in the grant. In addition to core partners, the project also integrates associate partners as an efficient means of enlarging the collection of viruses and reagents in the web-catalogue.

5.4. Resource distribution activity

Easy and efficient access to the viruses and reagents and to the service offered to the scientific community is attracting increasing numbers of requests for the products in the catalogue. In addition, the quality of the products distributed and the assistance provided by the management team to answer specific questions from scientists are establishing the EVAg as a key biological resource centre worldwide. It is now a recognised entity acting under the umbrella of medical and veterinarian international health organisations which include the WHO, GOARN, OIE and the major Centres for Disease Control and Prevention around the world which underpin the control of emerging viral diseases.

5.5. Access for end-users

To place an enquiry and receive a quotation for a product, open a web browser and type in “EVAg.” Then click on Login/Register to create an account. The online catalogue can then be accessed via the Portal link on the home page. Products in the catalogue can be found by typing in a keyword/and/or the appropriate taxonomic name. The filters on the right hand side of the Portal can also be used to browse through the products by category. The product(s) of interest should then simply be added to an enquiry cart, and the enquiry form should be completed. A Material Transfer Agreement (MTA) and a quotation for the products and shipping costs will then be sent to the end-user. The enquiry then becomes an order when the quote is accepted and the MTA is signed. All enquiries are evaluated in terms of biosafety, and an official (signed and stamped) end-user qualification form of the laboratory to receive and handle the products of interest is requested.

6. Contribution of the EVAg to the control of contemporary emerging viral diseases

The emergence of SARS at the end of 2002 has clearly demonstrated the lack of preparedness of countries to face emerging virus outbreaks. When the concept of EVA was discussed in 2008, this aspect of the consortium activity was clearly stated in the project submitted to the European Commission. This was reinforced in the second project: EVAg, submitted in 2013, with a contingency fund dedicated to support this activity.

6.1. Emergence of MERS coronavirus (MERS CoV) in the Arabian Peninsula

The emergence of the novel MERS-CoV in humans in Saudi Arabia in 2012 provided an opportunity for consortium partners and members of a European Epidemic Response Network to develop a precise and rapid MERS CoV diagnostic tool, suitable for field diagnosis under emergency conditions (Corman et al., 2012). During December 2012, the WHO recommended PCR assays as the method to detect the virus in blood samples, and identified the EVAg as a reliable source for the delivery of positive control reagents (WHO, 2018). To date more than 300 kits have been distributed worldwide, to 155 laboratories in 58 countries. This achievement demonstrated the capacity of the consortium to mobilize high-calibre scientists capable of rapidly developing and supplying a technical solution to a high-level emergency situation involving human pathogenic agents. Another key feature of this achievement was the efficiency of our logistics platform to distribute the material worldwide under the demanding conditions prevailing at the time.

6.2. Zika virus outbreak in South America

Zika virus emerged in French Polynesia and spread rapidly to South America and the Caribbean, causing at least 500,000 clinical cases, within the first year according to PAHO/WHO estimates. On the 1st of February 2016, WHO declared a Public Health Emergency of International Concern (PHEIC) (see Ref 2). On the 8th of February, the US Centre for Disease Control (USCDC) elevated its response to “level 1 activation” i.e. the highest level. Prior to May 2015, there were two strains of Zika virus in the EVAg online catalogue. By the first trimester of 2016, at the peak of international concern, partners had added eight more products of direct relevance to the emergency situation.

Since November, 2015, the EVAg has received 260 enquiries for more than 400 products to be distributed in 30 countries. A total of 168 products were provided in February, 2016 alone, with the highest demands in the USA, Singapore, Netherlands, Germany, France and China. In its interim guidance for Zika virus laboratory testing (March 23, 2016), WHO identified the EVAg as the provider for PCR quality-

control material (Corman et al., 2016). This emergency situation and the resulting need for a coordinated distribution logistic was very challenging. Consequently, the management team introduced procedures to alleviate the burden on partners and to improve product access. This was achieved by establishing additional distribution hubs for Zika virus products obtainable from: the Centre for Molecular Diagnostics and Therapy (CRIE), Moscow, Russia; Wuhan Institute of Virology (WIV), Wuhan, Southern China; National Institute of Infectious Diseases (NIID), Tokyo, Japan. The management team also negotiated a common Material Transfer Agreement (MTA), with industry on behalf of all consortium members and a centralised exchange logistics platform was established. This experience underlines the reality that anticipation and preparedness are key components for an effective response to public health emergencies.

6.3. Yellow fever outbreak in South America

From December, 2016 through May, 2017 Brazil reported its largest yellow fever (YF) outbreak in decades, with a total of 3240 suspected cases and 435 deaths (Fischer et al., 2017), prompting widespread yellow fever virus (YFV) vaccination campaigns and the need to distinguish between vaccine- and wild-type YFV-associated disease. Novel multiplex real-time reverse transcription PCRs that differentiate between vaccine and American wild-type YFV were developed by consortium partners in response to this outbreak and validated under field conditions (Fischer et al., 2017).

6.4. Integration of national Centres for Disease Control (CDCs) and RG4 biological safety laboratory networks

Centres for Disease Control (CDC) in countries play an important role for the control of virus outbreaks by the collecting data and samples during the identification phase of the pathogens. However the academic research combined with material collections appears to be an unavoidable actor for the preparedness and the control of an emerging virus disease, each time a variant form or a new form of a pathogen is responsible of it. Combining, in the same organization, CDC and high calibre research laboratories was foreseen as the best solution to reach both an efficient control of the virus propagation and a preparedness for the next outbreak.

At the same time, to cover the all range of pathogens from RG2 to RG4 was only made possible by the constitution of a group of high containment facilities within the organization.

Sixteen registered Biosafety Level-4 (BSL-4) laboratories, with the resources to handle the highest risk HG4 pathogens and five CDCs are partners or associate partners in the consortium. Each CDC contributes directly to the management and control of emerging virus diseases, under the umbrella of the WHO. The EVAg is also associated with the Global Outbreak Alert and Response Network (GOARN) and is recognised by GOARN as a supplier of high quality viruses and virus-related reagents and resources.

During the 2014–16 Ebola virus epidemics in West Africa, all of the BSL-4 institutes were directly involved in helping local authorities to contain the epidemic. They all gained important experience in the management of such health crises, collecting field samples and isolated relevant virus strains many of which are now characterised and stored in the facilities of the EVAg BSL-4 partner at the Bernard Nocht Institute in Hamburg, Germany. In addition, they addressed specific issues involving management of the exchange of high risk pathogens and activation of platforms dedicated to offering services to appropriate end-users.

7. Current status and future of the EVAg

The consortium is now in its third year of existence under the H2020 Framework Programme. Its ultimate objective is to become a

permanent archive that provides access to a very wide range of viruses and reagents globally. This will be achieved firstly, through extension of the funding arrangements, secondly through further increasing the range of contributors to the collection, and thirdly by bridging large European or international infrastructures having activities related to those of EVAg, including:

- European Research Infrastructure on Highly Pathogenic Agents (ERINHA); https://cordis.europa.eu/project/rcn/97132_en.html
- Infrastructures for Insect Disease Vector Research and Control (INFRAVEC); <https://infravec2.eu/>
- Biobanking and BioMolecular Resources Research Infrastructure (BBMRI); <http://www.bbMRI-eric.eu/faq/>
- Microbial Resource Research Infrastructure (MIRRI); <https://www.mirri.org/home.html>
- Network for Prevention and Control of animal diseases (VetBioNet); <https://www.vetbionet.eu>

7.1. Extension of the funding arrangements

It would be naive to suggest that the long-term survival of the consortium will be straightforward. For example, its perpetuation will require a continuous and increasingly large funding stream to meet the almost restrictive costs of research, laboratory development and upkeep in the face of newly emerging highly pathogenic viruses. Sustainability is a key issue for such an infrastructure and the consortium plan will be to remain a non-profit organization.

The obvious consequence of this fundamental choice is to have access to diversified sources of funding. The nations to which partners belong will have to support the collection activities including infrastructure management, as well as research concerning the development of new tools necessary to keep the archiving process up to date. The financial support for all the actions involved in preparedness for emerging viral diseases e.g., distribution of bio-resources to supply reagents to detect infected patients at local level will have to come from government health departments but at the international level, from the European Commission, charitable international health funding agencies such as the Wellcome Trust Foundation, the Bill and Melinda Gates Foundation, the WHO, the OIE. Future financial planning also includes the creation of a specific interface between the industrial sector and the consortium. In the first instance, this interface will explore bi-directional opportunities to organize scientific exchanges, priority access to bio-resources including reference material development of diagnostic services, validation of diagnostic assays and commercialization by industrial partners to the benefit of both parties. Signed contracts of collaboration will be facilitated, and procedures harmonized.

7.2. Expansion of the range of contributors to the collection

As noted above, the concept of the EVAg 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 advertise, inform, negotiate and conduct the entire transaction to the end-user via the web and internationally registered secure transportation companies. The reputations, high quality, experience and knowledge of the consortium partners, combined with the integration of the European Commission infrastructure, will provide end-users with opportunities to approach new fields of research in structural viral genomics, evolutionary biology, control of infectious diseases, anti-viral drug design, fundamental research, public and environmental health, pathogenesis, immunology and a wide variety of associated disciplines. Subsequently, subject to continuation of funding and the appropriate justification, the EVAg aims to extend the diversity of its disciplines to encompass fish, plant, bacterial, fungal, protist and other currently unrecognised viruses. This will be achieved first through expansion within the European Community, followed by integration of specialist

laboratories in the Americas, Russia, Asia, Southeast Asia, Australia and Africa. The recently created African CDC will provide a unique opportunity to establish strong links with public health institutes in Africa. The substance of this relationship will be based on trust and mutual benefit. For instance, training workshops and staff exchanges will be organized with the objective of developing appropriate infrastructures that can be directly integrated into the EVAg format and the levels of scientific expertise and quality and range of products that will justify their integration into EVAg as full partners within the consortium.

7.3. Looking to the future: integration with European and internationally established infrastructures

The EVAg provides a range of viruses and relevant reagents to end-users engaged in a wide variety of established infrastructures. For instance, the newly created EU infrastructure, INFRAVEC (European Infrastructures for Insect Disease Vector Research and Control - <https://infravec2.eu/>) supplies infectious vectors (e.g. mosquitoes and ticks) to their end-users. The EVAg is closely associated with this activity, via the provision of viruses that can infect the vectors. ERINHA (<http://www.erinha.eu/>), a European Strategy Forum on Research Infrastructures (ESFRI www.esfri.eu/), offering access to high containment facilities to industrial end-users for their preclinical trials including BSL4 pathogens, recommends EVAg as the provider of the viruses necessary for their trials. BBMRI, another ESFRI, plans to create a service unit dedicated to the provision of viruses and derived material from viruses. EVAg is identified as the recommended supplier.

The EVAg contributes to the functioning of other EU infrastructures involved in related research topics including zoonotic diseases, drug discovery, vaccine development, viral epidemiology and emerging virus diseases. These EU-funded projects include PREPARE (Platform for European Preparedness Against (Re-) emerging Epidemics - https://cordis.europa.eu/project/rcn/110174_en.html), COMPARE (Collaborative Management Platform for detection and Analyses of (Re-) emerging and foodborne outbreaks in Europe - <http://www.compare-europe.eu/about>), EMERGE (Efficient response to highly dangerous and emerging pathogens at EU level - <https://www.emerge.rki.eu/>), Zikalliance (a multinational and multidisciplinary research consortium coordinated by INSERM - <https://zikalliance.tghn.org/about/>). As a future objective, one can imagine the generation of links among all of these organisations to constitute a “Life Science Infrastructure Cooperative” dedicated to virology-related topics, in which the EVAg could play a central role.

For the long-term future, we are planning to establish closer collaborative links with other compatible scientific infrastructures by initiating teaching and training programmes amongst younger scientists to ensure that people of the right calibre will be able to undertake the roles currently occupied by experienced but “maturing” scientists. Indeed, one could envisage e-learning programmes being built into diploma courses in universities.

As we continue our ambitious mission to build a scientific infrastructure that can benefit scientists operating in all areas of the viral world, we recognise that other agencies and research teams can provide valuable datasets, and analytical expertise from which disease intervention strategies might be developed. Indeed, other compatible agencies are approaching the consortium to share their resources and to promote their activities through the consortium website. This is yet another avenue that is being explored, based on the complementarities of these parties with the existing group of partners.

At the time of writing, we are witnessing the massive impact of next-generation sequencing technology that will undoubtedly continue to evolve and provide even more discoveries, any one of which might then be exploitable by a future larger and more comprehensive form of agency. Since the first recognition of viruses and our obsession with trying to understand and control them, it has been an exciting time for virologists. Long may the EVAg and its successors ensure that this is always the case!

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.antiviral.2018.07.017>.

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