Pandemic Influenza Preparedness Framework for the sharing of influenza viruses and access to vaccines and other benefits

Decision WHA72(12), paragraphs 1(c), (d) and (e)

Report by the Director-General

March 2020

INTRODUCTION

1. In May 2019, the Health Assembly, in decision WHA72(12), requested the Director-General, inter alia:

> (c) to provide more information on the functioning, usefulness and limitations of the prototype search engine;
>
> (d) to explore, including through soliciting input from Member States, possible next steps in raising awareness of the PIP Framework among relevant databases and initiatives, data providers and data users, and in promoting the acknowledgment of data providers and collaboration between data providers and data users;
>
> (e) to continue providing information on new challenges posed and opportunities provided by new technologies in the context of the Pandemic Influenza Preparedness Framework for the sharing of influenza viruses and access to vaccines and other benefits and possible approaches to them.

The present draft report addresses these three requests. In line with decision WHA72(12) it is submitted in order to garner relevant input from Member States, following which it will be finalized.

2. Paragraphs 1(c) and (d) relate, directly or indirectly, to the handling of genetic sequence data under the Pandemic Influenza Preparedness (PIP) Framework for the sharing of influenza viruses and access to vaccines and other benefits. Although considerable work has already been undertaken on this matter by the PIP Advisory Group further to its mandate under section 5.2.4 of the Framework, discussions are ongoing. The Health Assembly is invited to consider the information in this report and to provide guidance on the next steps. Paragraph 1(e) looks to the challenges posed and the opportunities that new technologies may provide for the evolution of the WHO's work in influenza preparedness, including implementation of the PIP Framework.

BACKGROUND

Genetic sequence data under the PIP Framework

3. The PIP Framework is an access and benefit-sharing arrangement that covers the sharing of influenza viruses with human pandemic potential and other materials, collectively defined as PIP biological materials, on the one hand, and access to benefits arising from such sharing, on the other.[1]

4. Genetic sequence data from Influenza viruses with pandemic potential are not included in the definition of PIP biological materials.

5. The handling of genetic sequence data from influenza viruses with pandemic potential under the PIP Framework has gained importance given the growing use of synthetic biology technologies, which enable influenza virus proteins, antibodies and candidate vaccine viruses to be produced using only genetic sequence data.

Expectations concerning genetic sequence data under the PIP Framework

6. The PIP Framework sets out several expectations concerning genetic sequence data from influenza viruses with pandemic potential. These include requirements for laboratories that are part of the Global Influenza Surveillance and Response System to submit genetic sequence data from influenza viruses

[1] For the definition of PIP biological materials, see WHO. Pandemic influenza preparedness framework for the sharing of influenza viruses and access to vaccines and other benefits. Geneva: World Health Organization; 2011, Section 4.1 (https://apps.who.int/iris/handle/10665/44796).

with pandemic potential to the Global Initiative on Sharing All Influenza Data (GISAID) and GenBank or similar databases in a timely manner,[1] and to share analyses and sequences in a rapid, timely and systematic manner with the originating laboratory and among laboratories within the Global Influenza Surveillance and Response System.[2] The Framework further specifies that WHO Collaborating Centres for influenza are to upload genetic sequence data from influenza viruses with pandemic potential to a "publicly accessible database in a timely manner but no later than three months after sequencing is completed, unless otherwise instructed …".[3]

Use of genetic sequence data from Influenza viruses with pandemic potential and benefit sharing under the PIP Framework

7. The PIP Framework has two main benefit-sharing mechanisms: the Standard Material Transfer Agreement 2 and the Partnership Contribution. Specific requirements must be fulfilled for each mechanism to be triggered: the need for a Standard Material Transfer Agreement 2 is triggered when an entity receives PIP biological materials from the Global Influenza Surveillance and Response System, and the need for a Partnership Contribution is triggered when the Global Influenza Surveillance and Response System is used by an influenza vaccine, diagnostic or pharmaceutical manufacturer.[4]

8. There is therefore no obligation to conclude a Standard Material Transfer Agreement 2 with WHO when genetic sequence data from influenza viruses with pandemic potential are used because no PIP biological material is received by the user.

9. However, in developing the parameters for implementation of the Partnership Contribution expected from certain manufacturers,[5] use of the Global Influenza Surveillance and Response System was deemed to include use of genetic sequence data from influenza viruses with pandemic potential. The annual Partnership Contribution questionnaire therefore includes questions about the use of genetic sequence data from influenza viruses with pandemic potential[6] as a factor for identifying manufacturers.

PIP Framework Advisory Group work on genetic sequence data

10. In 2013, the PIP Advisory Group, recognizing the importance of genetic sequence data from influenza viruses with pandemic potential and in keeping with its mandate, began to address the handling of genetic sequence data from influenza viruses with pandemic potential under the Framework.[7] In the course of its work,[8] the Advisory Group highlighted the importance of four key principles in relation to handling genetic sequence data from influenza viruses with pandemic potential under the Framework:[9]

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[1] PIP Framework, Annex 4, paragraph 9.
[2] PIP Framework, Section 5.2.1.
[3] PIP Framework, Annex 5, Terms of Reference for WHO Collaborating Centres for influenza Core terms of reference: Section B.5.
[4] See PIP Framework, Section 4.3 for a definition of this term.
[5] See PIP Framework, Section 6.14.3.
[6] PIP Framework Partnership Contribution Questionnaire – 2020. Geneva: World Health Organization; 2020 (https://www.who.int/influenza/pip/partnership_contribution/PC-Questionnaire-2020/en/, accessed 12 March 2020).
[7] PIP Framework, Section 5.2.4.
[8] Advisory Group's work on handling genetic sequence data under the PIP Framework. Geneva: World Health Organization, available at https://www.who.int/influenza/pip/advisory_group/gsd/en/ (accessed 12 March 2020).
[9] Approaches to seasonal influenza and genetic sequence data under the PIP Framework: analysis. Geneva: World Health Organization; 2018: paragraph 65(c) (https://www.who.int/influenza/pip/WHA70108b_Analysis.pdf, accessed 12 March 2020).

(1) rapid sharing of high-quality genetic sequence data for timely risk assessment and response;
(2) sustainable, public access to genetic sequence data from influenza viruses with pandemic potential;
(3) fair and equitable sharing of benefits arising from the sharing of genetic sequence data;
(4) acknowledgment of data providers and active collaboration between data providers and data users.

11. In October 2018, the PIP Advisory Group recommended that the Director-General implement two actions. The first was to pilot a search engine that had been previously developed in order to identify products that had potentially made use of genetic sequence data from influenza viruses with pandemic potential but might not be subject to benefit sharing. The second was to explore the next steps in implementing the principle of acknowledgment of data providers and active collaboration between data providers and users. In particular, the Advisory Group recommended that this involve developing appropriate language for databases to consider using in order to inform their potential users of genetic sequence data from influenza viruses with pandemic potential and the PIP Framework.[1]

Mandate under decision WHA72(12)

12. In May 2019, the Health Assembly, noting the PIP Advisory Group's October 2018 recommendations to the Director-General, requested, inter alia, the Director-General:

> […]
>
> (c) to provide more information on the functioning, usefulness and limitations of the prototype search engine;
>
> (d) to explore, including through soliciting input from Member States, possible next steps in raising awareness of the PIP Framework among relevant databases and initiatives, data providers and data users, and in promoting the acknowledgment of data providers and collaboration between data providers and data users;
>
> […].

The following parts deal with different aspects.

PART I. INFORMATION ON THE FUNCTIONING, USEFULNESS AND LIMITATIONS OF THE PROTOTYPE SEARCH ENGINE (DECISION WHA72(12), PARAGRAPH 1(c))

Background

13. In the course of its work on genetic sequence data, the PIP Advisory Group identified the optimal characteristics of a system for handling genetic sequence data from influenza viruses with pandemic potential under the PIP Framework.[2] In connection with this work, the PIP Advisory Group considered systems to monitor the use of genetic sequence data from influenza viruses with pandemic potential in

[1] Meeting of the PIP Framework Advisory Group, 17-19 October 2018, Geneva, Switzerland. Geneva: World Health Organization; 2018: paragraphs 64 and 65 (https://www.who.int/influenza/pip/AGMR_Oct2018.pdf?ua=1, accessed 12 March 2020).

[2] See Optimal characteristics of an influenza genetic sequence data sharing system under the PIP Framework. Geneva: World Health Organization; June 2016 (https://www.who.int/influenza/pip/advisory_group/twg_doc.pdf?ua=1, accessed 12 March 2020).

end-products.[1] To this end, it recommended that the Secretariat continue its collaboration with the World Federation for Culture Collections and the WFCC-MIRCEN World Data Centre for Microorganisms.[2] The search engine relies on data contained in publicly available platforms such as scientific publications, patents, clinical trial files and regulatory approval files. More detailed information on these two organizations can be found in Annex 1.

14. The search engine builds on the World Data Centre for Microorganisms' considerable experience in data management systems, including tools for automatic extraction of information to organize, make public and explore the data contained in data collections.

15. The World Data Centre for Microorganisms developed the search engine platform, and the Secretariat provided technical guidance on its implementation. At the request of the PIP Advisory Group, the search engine was piloted to assess its usefulness and feasibility for collecting data and identifying potential benefit-sharing opportunities.[3]

16. In May 2019, the Health Assembly requested the Director-General to provide more information on the functioning, usefulness and limitations of the prototype search engine.

Functioning of the prototype search engine

17. Through a series of questions and answers, the following section provides an overview of the functioning of the prototype search engine. In addition, an illustration of how the search engine works can be found in Annex 2.

Search engine overview

Where is the search engine housed and who owns the data it uses or generates?

18. The search engine platform is housed at the World Data Centre for Microorganisms. All data used in searches are taken from public data sources and transferred into the engine. All data and search results are therefore collations of publicly available information.

Who operates and maintains the search engine?

19. The World Data Centre for Microorganisms operates and maintains the platform. Updates to the data are conducted both automatically and manually, depending on the data sources. Some sources have to be regularly updated by the Centre, whereas other data sources allow for automatic updates. The frequency of the update cycle is determined by WHO, and updates can be carried out as regularly as needed.

[1] Meeting of the PIP Framework Advisory Group, Consolidated Version: 21-24 October 2014, Geneva, Switzerland. Geneva: World Health Organization; 2014: paragraph 32. (https://www.who.int/influenza/pip/advisory_group/oct2014_mr_consolidated.pdf?ua=1, accessed 12 March 2020).

[2] See Meeting of the PIP Framework Advisory Group. Geneva: World Health Organization; April 2015: paragraph 30 (https://www.who.int/influenza/pip/pip_ag_april2015_meetingreport.pdf?ua=1, accessed 12 March 2020); and Meeting of the PIP Framework Advisory Group. Geneva: World Health Organization; April 2016: paragraph 55 https://www.who.int/influenza/pip/ag_april2016_MeetingRpt.pdf?ua=1, accessed 12 March 2020).

[3] Meeting of the PIP Framework Advisory Group. Geneva: World Health Organization; April 2016: paragraph 55 (https://www.who.int/influenza/pip/ag_april2016_MeetingRpt.pdf?ua=1, accessed 12 March 2020).

Who can use the engine and is special access needed?

20. Currently only authorized users have access through a log-in process that requires a username and password.

How does the search engine link to the PIP Framework Influenza Virus Traceability Mechanism?

21. Information on influenza viruses with pandemic potential and subtypes is taken from the Influenza Virus Traceability Mechanism for the purposes of formulating searches. Regular and automatic updating of the virus list and subtypes would require the Influenza Virus Traceability Mechanism to have a shared interface with the search engine. This could be envisaged in the future if the search engine is deemed to be a useful tool.

Search function and resulting data

Which terms can be searched for?

22. It is possible to search for any influenza virus with pandemic potential (e.g. A/H5N1) and/or any subtype (e.g. A/Anhui/1/2005) included in the Influenza Virus Traceability Mechanism. Virus or subtype searches can be conducted broadly through the basic search function, or narrowed down using one of the following fields: nucleotide sequences, publications, patents, clinical trial files and regulatory approval files (see Annex 2 for an illustration).

How are data pulled from the various sources?

23. When a search is conducted, the engine mines data for each keyword in all publicly available data sources for the fields it covers (nucleotide sequences, publications, patents, clinical trial files and regulatory approval files) and transfers the information it finds into the search engine. The search engine can currently only search publicly accessible databases that are not covered by a data access or similar user agreement.

In what languages are searches conducted?

24. Currently, the content is in English and searches are limited to English. However, the platform interface could be provided in other languages.

What types of results are generated?

25. Once a search is conducted, the user is directed to a page that contains all the publicly available information found on that virus and/or subtype. The engine can, for instance, provide the user with a list of all sequences developed from the virus and/or the subtype, in addition to all publications, regulatory files and patent applications that mention that virus and/or subtype. Each search result provides the user with a hyperlink to the original data source (see Annex 2 for further information).

How are reports generated and presented?

26. The prototype search engine does not currently generate reports. This means that if, for instance, the user wishes to know which entities have used genetic sequence data from influenza viruses with pandemic potential to develop influenza products, each of the links—for instance to regulatory files, patent applications or clinical trial files—must be reviewed individually and a report created manually. The World Data Centre for Microorganisms has confirmed that it would be technically feasible to enhance the prototype search engine by adding a function to automatically generate reports. Likewise, the Centre has confirmed that it could develop additional features to allow results to be exported in Excel format, making the search engine more useful and user-friendly.

Usefulness of the search engine

27. The search engine is still a prototype and, as such, its functions are limited to the specific purpose for which it was developed – to identify end-products that have been developed with genetic sequence data from influenza viruses with pandemic potential. The engine was piloted in mid-2016. If the tool is deemed useful, it could be expanded, more functions could be added, and existing functions improved. This section will first assess the usefulness of the search engine with regard to its intended purpose, and then explore some potential improvements to enhance and/or expand its uses and features.

Assessment of the search engine's usefulness

28. The search engine's primary purpose is to monitor the use of genetic sequence data from influenza viruses with pandemic potential in the development of influenza-related end-products (such as vaccines, antiviral medicines and diagnostic products), so that entities that have used genetic sequence data from influenza viruses with pandemic potential to develop such products can be identified.

29. The pilot phase in mid-2016 resulted in the identification of 10 end-products manufactured using genetic sequence data from influenza viruses with pandemic potential by eight companies that are not listed in the Influenza Virus Traceability Mechanism because they did not receive PIP biological materials.[1]

30. The search engine pilot proved to be an effective tool for identifying entities that used genetic sequence data from influenza viruses with pandemic potential for the manufacture of end-products. As more fully explained in the following paragraphs, this enabled the Secretariat to identify entities that would not otherwise have been identified, and that would not necessarily know about the PIP Framework, its objectives, or its benefit-sharing mechanisms.

Standard Material Transfer Agreement 2

31. The Standard Material Transfer Agreement 2 is a legally binding agreement between WHO and a recipient[2] of PIP biological materials from a laboratory within the Global Influenza Surveillance and Response System. Conclusion of an Agreement with WHO is linked to receipt of physical material by an entity that is not part of the Global Influenza Surveillance and Response System. Since genetic sequence data from influenza viruses with pandemic potential are not included in the definition of PIP biological materials, use of genetic sequence data from influenza viruses with pandemic potential does not trigger the obligation to enter into a Standard Material Transfer Agreement 2 with WHO.

32. The search engine could be a useful tool for monitoring the development of influenza products that could be important for influenza prevention and control. These products may be manufactured by companies that have not received PIP biological materials, and thus are not recorded in the Influenza Virus Traceability Mechanism, but that could be interested in supporting the work of WHO under the PIP Framework.

Partnership Contribution

33. The Partnership Contribution is an annual cash contribution that is based, inter alia, on "use of the Global Influenza Surveillance and Response System"[3] by manufacturers of influenza vaccine,

[1] Presentation to the PIP Framework Advisory Group, 14 October 2016. Geneva: World Health Organization;2016: slides 13–14 (working document, not published).
[2] PIP Framework, Annex 2, footnote 1.

[3] "Use of the Global Influenza Surveillance and Response System" means that a company or institution used or received: (1) materials (e.g. virus materials, such as candidate vaccine viruses, wild-type viruses, complementary DNA, plasmids, or reagents); and/or (2) services (e.g. antigenic and genetic characterization of candidate vaccine viruses/seed material, antiviral susceptibility assays); and/or (3) information (e.g. sequence information,

diagnostic or pharmaceutical products. When determining who should pay the Partnership Contribution, use of genetic sequence data from influenza viruses with pandemic potential is deemed to constitute use of the Global Influenza Surveillance and Response System. Manufacturers that have used genetic sequence data from influenza viruses with pandemic potential to develop, test or produce a licensed influenza product are therefore expected to make an annual contribution.

34. The starting point for identifying companies that have used the Global Influenza Surveillance and Response System is the Influenza Virus Traceability Mechanism, which records all recipients of PIP biological materials. Using the data in the Mechanism, as well as other data gathered by the Secretariat through internet searches, the Secretariat issues an annual questionnaire to identify "influenza vaccines, diagnostic and pharmaceutical manufacturers"[1] that use or have used the Global Influenza Surveillance and Response System.

35. Monitoring the use of genetic sequence data from influenza viruses with pandemic potential by companies through the search engine could help to identify potential partnership contributors, complementing the WHO processes outlined above.

Potential developments to enhance the search engine's usefulness

36. As mentioned, the prototype search engine was developed for a specific purpose. Thus far, it has only been piloted once to determine whether it fulfils its function with regard to searching for influenza viruses with pandemic potential.

37. In further discussions with the developers, three ideas were raised regarding possible changes to the search engine. They are outlined below.

    (a) *Create an automatic link from the search engine to the Influenza Virus Traceability Mechanism*: there is presently no automatic link between the two databases. It would be technically feasible to create an interface between the two platforms. Doing so could be useful for both systems, as it would allow the search engine to automatically update its list of viruses and subtypes, while providing the Influenza Virus Traceability Mechanism with new functions. For instance, it could be possible for a user to click on a virus name or a subtype in the Influenza Virus Traceability Mechanism and be redirected to the search engine, which could then generate more information and metadata on that virus or subtype. The search engine could also be used by the broader scientific community to connect researchers around the world, enhancing cooperation among scientists and encouraging technology transfer. As with the Global Catalogue of Microorganisms (see Annex 1), the WHO search engine could be opened to the public, fostering accessibility to information and data on influenza viruses and related research.

    (b) *Link the search engine to databases covered by access or user agreements:* some publicly accessible databases require users to register and accept an agreement on data access and use before they are granted access. For the search engine to retrieve data from such databases, terms would need to be negotiated and access granted by the database in question. Doing so would not change the need for data users to agree to separate data access and user agreements for their individual use.

    (c) *Broaden the search engine's parameters:* it would be technically feasible to broaden searches to include more pathogens or more users. The additional parameters would be determined in discussions with Member States.

Limitations of the prototype search engine

epidemiological data, antiviral susceptibility data, pre- and post-vaccine composition meeting reports); developed and/or provided by or through the Global Influenza Surveillance and Response System.

[1] PIP Framework, Section 4.3.

38. The search engine has both intrinsic limitations and technical and/or software limitations.

Intrinsic limitations

39. Monitoring use of genetic sequence data from influenza viruses with pandemic potential in end-products relies on users clearly and consistently identifying the sequences they use in publications, patent applications, regulatory approval files and clinical trial files. This can be done through different methods, including using a unique identifier, using the name of the virus, or providing a database accession number.[1]

40. Even though disclosure of data is a common requirement for scientific publications, patent applications, clinical trial files and regulatory approval files, there is currently no consistent practice of identifying genetic sequence data using a database accession number or other unique identifier. In addition, in some cases, the data are considered to be confidential.

41. Lastly, some databases cannot be included in data mining searches as they require users to register and accept a data access and user agreement before they are granted access to the data contained in the database – and the data contained in these databases are covered by terms and conditions that affect how they can be published or shared with individuals or entities that have not signed the data access and user agreement. For the search engine to retrieve data from such databases, terms would need to be negotiated and access granted by the relevant databases.

42. For the above reasons, the search engine has intrinsic limitations owing to external factors that are beyond the control of WHO and/or the developers.

43. Despite these limitations, the search engine is potentially a useful tool for the PIP Framework. It could not only support the Secretariat's work to implement its benefit-sharing objectives but also be used as a potential tool for connecting researchers around the globe, by facilitating access to influenza virus information and enhancing cooperation among scientists.

Software limitations

44. Some software/platform limitations were identified during the pilot phase. They are outlined below.

    (a) *Duplications*: the search engine results sometimes show the same patent (i.e. with the same publication number) repeatedly, particularly for certain virus subtypes. This created additional work for the user to be able to retrieve and use the search results. The issue has been discussed with the developers, who confirmed that there are ways to improve the software so that duplications are avoided and/or limited.
    (b) *Inability to auto-generate reports and export data to Microsoft Excel (or other data analysis tools)*: as mentioned above, the interface can be improved, and more automatic functions added. Developers would need further instructions from the Secretariat to assess the time and funds required to implement such improvements.
    (c) *Lack of an automatic link to the Influenza Virus Traceability Mechanism*: addressing this would require an interface to be established between the search engine and the Influenza Virus Traceability Mechanism. The developers confirmed that it is technically feasible, but it would require further discussion with the Influenza Virus Traceability Mechanism software developers.

Conclusions

[1] Options to monitor the use of genetic sequence data from influenza viruses with human pandemic potential (IVPP GSD) in end-products – 6 May 2016. Geneva: World Health Organization; 2016: page 8 (https://www.who.int/influenza/pip/advisory_group/gsdoptionspaper_revised.pdf?ua=1, accessed 12 March 2020).

45. Overall, the results of the search engine's pilot phase were positive. Results were generated, and several areas for improvement were identified – notably to reduce the level of human intervention required to collate results and generate reports. Upon further discussion with the developers, it seems like all the current software limitations can be improved and/or overcome. Costs and timelines for these improvements will be discussed in detail with the World Federation for Culture Collections and the World Data Centre for Microorganisms if Member States determine that the search engine's potential should be explored further.

46. The search engine still has some intrinsic limitations, although there are ways to expand the range of information that can be retrieved by the search engine, such as by negotiating data access and user agreements with relevant databases. Nevertheless, the search engine clearly cannot be transformed into a tool to monitor all uses of genetic sequence data from influenza viruses with pandemic potential by companies.

PART II. OPTIONS TO RAISE AWARENESS OF THE PIP FRAMEWORK AMONG REPRESENTATIVES OF DATABASES AND OTHER INITIATIVES, DATA PROVIDERS AND DATA USERS (DECISION WHA72(12), PARAGRAPH 1(d))

47. As part of its work on the handling of genetic sequence data under the PIP Framework, the PIP Advisory Group surveyed and met several times with representatives of databases and other initiatives.[1] These representatives are invited to participate in the biannual consultations that the PIP Advisory Group holds with PIP Framework stakeholders, under Section 6.14.6.

48. There are several ways to raise awareness among representatives of databases and other initiatives, data providers and data users of not only the PIP Framework, but also the Global Influenza Surveillance and Response System and its global work to prevent and control influenza. This would create greater understanding of, and appreciation for, the significant value of the genetic sequence data and associated metadata generated by laboratories within the Global Influenza Surveillance and Response System.

Outreach to databases and other initiatives

49. The first option is to broaden direct outreach to databases and other initiatives that house genetic sequence data from influenza viruses. Outreach would enable the Secretariat to present the PIP Framework and its objectives, and discuss the feasibility, advantages and disadvantages of flagging genetic sequence data from influenza viruses with pandemic potential in their databases.

50. By raising awareness of the PIP Framework, users could be sensitized to the critical work of the Global Influenza Surveillance and Response System in preventing and controlling influenza.

[1] See for example: WHO Survey on the Sharing of Genetic Sequence Data of Influenza Viruses with Human Pandemic Potential: Results and Analysis of Data Received. Geneva: World Health Organization; April 2016 (https://www.who.int/influenza/pip/advisory_group/GSDSurveyResults.pdf?ua=1, accessed 12 March 2020); Comments Received on the Draft Document 'Optimal Characteristics of an Influenza Genetic Sequence Data Sharing System under the PIP Framework'. Geneva: World Health Organization; 2015 (https://www.who.int/influenza/pip/advisory_group/twg_comments/en/, accessed 12 March 2020); Technical Expert Working Group on Genetic Sequence Data. Final Report to the PIP Advisory Group. Geneva: World Health Organization; October 2014 (https://www.who.int/influenza/pip/advisory_group/PIP_AG_Rev_Final_TEWG_Report_10_Oct_2014.pdf?ua=1), accessed 12 March 2020).

51. Many publicly accessible databases already contain notification statements (e.g. general statements that data may be subject to third-party intellectual property rights, or biodiversity-related access and benefit-sharing requirements) or are accessible subject to acceptance of a data access agreement.[1]

52. A statement on the PIP Framework could be included in existing notification statements, or a new statement could be added, providing an easy and inexpensive option to make users aware of the PIP Framework and its objectives. In addition, sequences from influenza viruses with pandemic potential could be flagged to make users aware of the link to the PIP Framework and its objectives.

Outreach to journals

53. Given the close linkages between databases and journals, another approach is to reach out to editors of journals or specialized peer-reviewed periodicals in order to present the PIP Framework and its objectives. This would support the suggestion made by the PIP Advisory Group's Technical Working Group on sharing influenza genetic sequence data that the Secretariat should promote acknowledgement of data providers by journals so that they undertake to acknowledge the contributions of data providers, as well as originating laboratories, in scientific publications and other works.[2]

54. This approach would also enable a deeper understanding of the value of genetic sequence data from influenza viruses with pandemic potential.

Outreach to data providers and data users

55. Lastly, targeted information and education outreach through social media, universities or the future WHO Academy could be used to raise awareness of the PIP Framework, the Global Influenza Surveillance and Response System and the value of genetic sequence data from influenza viruses with pandemic potential. Broad outreach could shed greater light on the value of the work undertaken by data providers and databases.

PART III. NEW CHALLENGES POSED AND OPPORTUNITIES PROVIDED BY NEW TECHNOLOGIES IN THE CONTEXT OF THE PIP FRAMEWORK AND POSSIBLE APPROACHES TO THEM (DECISION WHA72(12), PARAGRAPH 1(e))

56. In March 2019, WHO launched the Global influenza strategy 2019–2030.[3] The strategy provides an overarching framework for the Secretariat, Member States and partners to approach influenza holistically through the establishment and strengthening of capacities to prevent, control and prepare for influenza epidemics and pandemics at the global, regional and national levels. Recognizing that current prevention and control tools have limitations (e.g. suboptimal effectiveness and annual requirement for seasonal influenza vaccines and limited options for treatment of severe influenza), the strategy highlights an urgent need for better tools to prevent, detect, control and treat influenza. Therefore, the first high-level outcome for 2030 is to promote development of better global tools, such that a focused, consensus-driven plan leads to greater research, innovation and availability of new and improved tools.

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[1] See for example: EMBL-EBI Terms of Use (https://www.ebi.ac.uk/about/terms-of-use/, accessed 12 March 2020); GISAID EpiFlu™ Database Access Agreement (https://www.gisaid.org/registration/terms-of-use/, accessed 12 March 2020).

[2] Options to monitor the use of genetic sequence data from influenza viruses with human pandemic potential (IVPP GSD) in end-products. Geneva: World Health Organization; 2016: 9 (https://www.who.int/influenza/pip/advisory_group/gsdoptionspaper_revised.pdf?ua=1, accessed 12 March 2020).

[3] WHO. Global influenza strategy 2019–2030. Geneva: World Health Organization; 2019 (https://apps.who.int/iris/handle/10665/311184).

57. Through the Global influenza strategy, as well as implementation of decision WHA72(12), paragraph 1(e), the Secretariat is committed to tracking the development of new and improved technologies and informing Member States of the challenges and opportunities that these technologies may pose. In June 2019, to begin implementing measures to achieve the high-level outcome of promoting development of better global tools, the Secretariat hosted a technical consultation on influenza product research and innovation. The consultation allowed the Secretariat and participants from Member States, industry, academic institutions and civil society: to review the product landscape and current trends in the production and use of influenza vaccines, antiviral agents and other treatments; and to identify concrete actions and opportunities for WHO and partners to accelerate research and innovation for better global tools. Participants discussed a set of 10 considerations to strengthen the research and innovation ecosystem for influenza. The Secretariat is planning follow-up activities, including workshops dedicated to prioritizing research into new and repurposed treatments for influenza and assessing the impact of prior immunization on the effectiveness of seasonal influenza vaccines.

58. Additionally, as part of the monitoring and evaluation under the Global influenza strategy, the Secretariat plans to release biennial reports on the progress towards the development of better global tools. The first report will be released in late 2020. These reports will assess the landscape and pipeline for: new technologies; research trends; global production capacities; and global, regional and national initiatives that aim to accelerate research and innovation to create better global tools for influenza. These reports will also fulfil the request made to the Secretariat in decision WHA72(12), paragraph 1(e) by including information on the challenges posed and opportunities provided by new technologies in the context of the PIP Framework.

ANNEX 1

Background information on the World Federation for Culture Collections, the World Data Centre for Microorganisms and the Global Catalogue of Microorganisms

World Federation for Culture Collections

1. The World Federation for Culture Collections is a multidisciplinary commission of the International Union of Biological Sciences and a federation within the International Union of Microbiological Societies. It is involved in the collection, authentication, maintenance and distribution of cultures of microorganisms and cultured cells, aiming to promote and support the establishment of culture collection and related services.[1]

World Data Centre for Microorganisms

2. To accomplish its mission, the World Federation for Culture Collections developed an international database on culture resources worldwide, which became the World Data Centre for Microorganisms. The World Data Centre for Microorganisms began by publishing the world directory of collections of cultures of microorganisms in 1972, and the database was made available online in the late 1990s. There are now 789 collections in 77 countries and regions registered in the Centre's directory of collections, known as CCINFO.[2] The Centre is currently hosted by the Institute of Microbiology at the Chinese Academy of Sciences.

Global Catalogue of Microorganisms

3. To help culture collections to establish an online catalogue and provide users with a system with fast, accurate and convenient data accessibility, the World Data Centre for Microorganisms launched the Global Catalogue of Microorganisms in 2012.[3] The Catalogue is a robust, reliable and user-friendly system to help culture collections manage, disseminate and share information related to their holdings.[4] Furthermore, it provides a uniform interface for scientific and industrial communities to access comprehensive microbial resource information.

4. The Global Catalogue of Microorganisms covers bacteria, fungi, algae, antibodies, Archaea, cyanobacteria, phages, plasmids, protozoa and viruses. Data are provided by partners on a voluntary basis. With 131 collections from 49 countries, the Global Catalogue of Microorganisms has become one of the largest international cooperation projects in the field of microbial resources, fostering accessibility to microbial resources and their utilization worldwide.

5. Collections are expected to provide a minimum amount of information about organisms, but it is up to the collection to decide which information they want to share. Before data are published on the Global Catalogue of Microorganisms' webpage, the data management system performs automatic data quality controls, including validation of the data format and contents. In addition, the Global Catalogue of Microorganisms contains not only the catalogue information from culture collections, but also knowledge on strains and species extracted from public databases. It is not currently possible to order

[1] For more information on the World Federation for Culture Collections, see http://www.wfcc.info/ (accessed 8 April 2020).
[2] See http://www.wfcc.info/ccinfo/ (accessed 8 April 2020).
[3] The Global Catalogue of Microorganisms is available at http://gcm.wfcc.info/ (accessed 8 April 2020).
[4] The Global Catalogue of Microorganisms website reports that only about one sixth of collections have an online catalogue, hindering the visibility and accessibility of microbial strains.

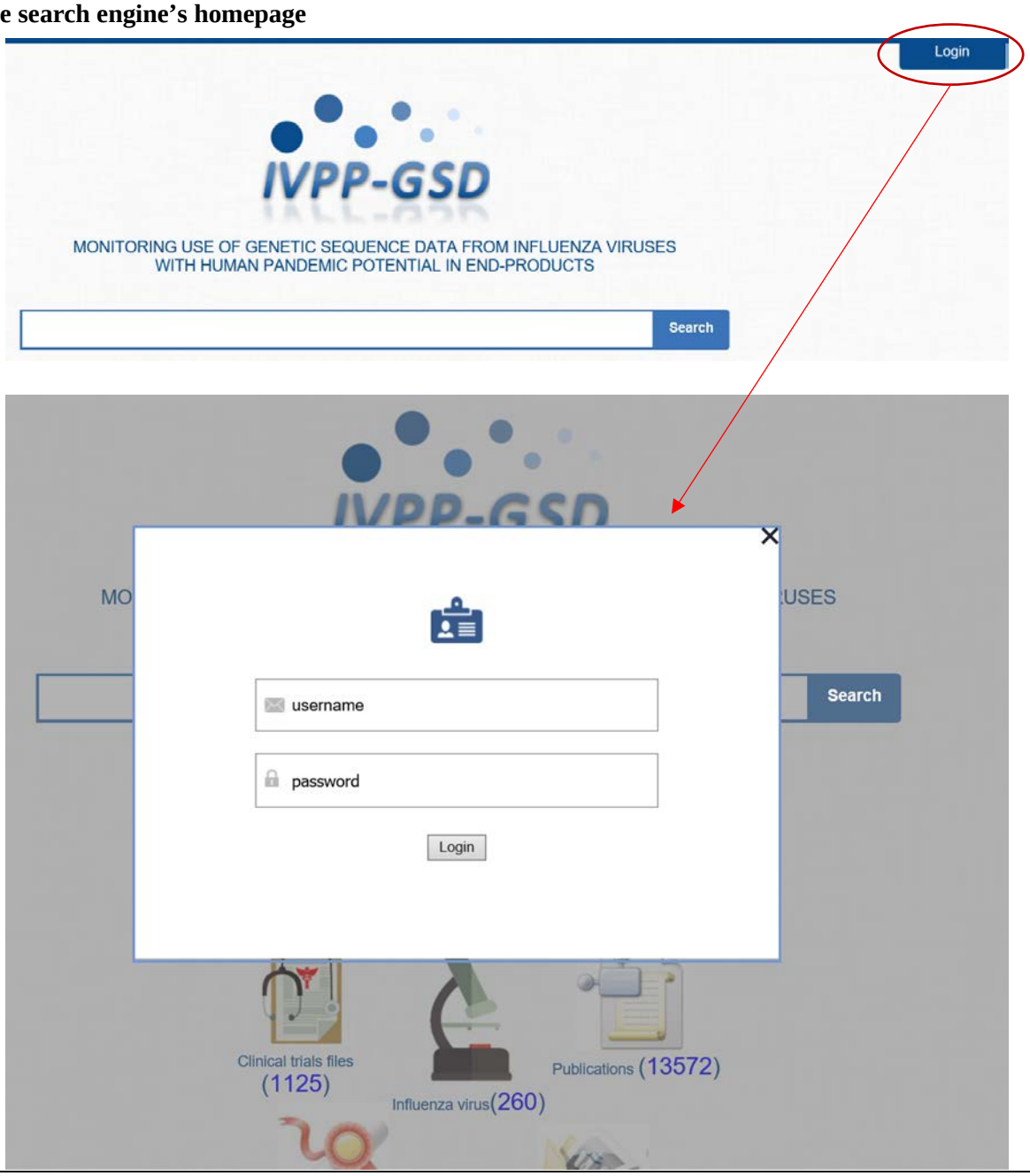
strains from the Catalogue, which only provides information on strains. It is up to the interested entity to contact the relevant collection for sourcing purposes.

ANNEX 2

Illustration of the WHO search engine

In order to enable readers to better understand how the search engine works, a series of examples is presented below with illustrative screen shots.

The search engine's homepage



1. Once the user has logged in, a search can be conducted using one of the six tabs available: (1) basic search; (2) nucleotide sequences; (3) publications; (4) patents; (5) clinical trial files; and (6) regulatory approval files.
2. In the following example, a search for "H5N1" was conducted in the "**Basic Search**" tab.

Example 1. Entering a term into the "Basic Search" tab

When a basic search is launched (e.g. H5N1), the search engine finds all the subtypes of that virus and all the sequences, publications, patents, clinical trial files and regulatory approval files that mention the virus. As illustrated below, the search engine provides all the information it has found in each category used for the search (note that each illustration lists only a small portion of the results found, e.g. five out of 465 for sequences).

Example 1. Search results for "H5N1" in "Basic Search"

(a) Subtypes

Search Result for:"H5N1"

	A/Anhui/1/2005	A/Bangladesh/103/2012	A/Bangladesh/154/2012
	A/Bangladesh/8002/2013	A/Cambodia/P0322095/2005	A/Cambodia/Q0321176/2006
A/H5N1:	A/Cambodia/R0405050/2007	A/Cambodia/S1211394/2008	A/Cambodia/U0417030/2010
	A/Cambodia/V0203306/2011	A/Cambodia/V0401301/2011	A/Cambodia/V0417301/2011
	A/Cambodia/V0606311/2011	A/Cambodia/W011303/2012	A/Cambodia/W0329318/2012

(b) Nucleotide sequences

Order	Definition	accession1	GI	Year	Length	Link
1	Influenza A virus (A/Indonesia/CDC184/2005(H5N1)) segment 4 sequence	CY014197	113494675	2006	1659	NCBI Openflu
2	Influenza A virus (A/Indonesia/CDC194P/2005(H5N1)) segment 4 sequence	CY014168	113494680	2006	1659	NCBI Openflu
3	Influenza A virus (A/Indonesia/CDC287T/2005(H5N1)) segment 4 sequence	CY014199	113494692	2006	1659	NCBI Openflu
4	Influenza A virus (A/Indonesia/CDC292N/2005(H5N1)) segment 4 sequence	CY014200	113494697	2006	1659	NCBI Openflu
5	Influenza A virus (A/Indonesia/CDC326N2/2006(H5N1)) segment 4 sequence	CY014203	113494717	2006	1659	NCBI Openflu

1 to 5， total 465 prve next

(c) Publications

Order	Paper Title	Journal	Year	Link
1	Reliability of pseudotyped influenza viral particles in neutralizing antibody detection.	PLoS ONE	2014	PubMed
2	Inhibitory activities of 3-trifluoromethyl benzamide derivatives against the entry of H5N1 influenza viruses	Nan Fang Yi Ke Da Xue Xue Bao	2014	PubMed
3	A Replicating Modified Vaccinia Tiantan Strain Expressing an Avian-Derived Influenza H5N1 Hemagglutinin Induce Broadly Neutralizing Antibodies and Cross-Clade Protective Immunity in Mice.	PLoS ONE	2013	PubMed
4	A single residue substitution in the receptor-binding domain of H5N1 hemagglutinin is critical for packaging into pseudotyped lentiviral particles.	PLoS ONE	2012	PubMed
5	Homologous and heterologous antibody responses to a one-year booster dose of an MF59(Â®) adjuvanted A/H5N1 pre-pandemic influenza vaccine in pediatric subjects.	Hum Vaccin Immunother	2012	PubMed

1 to 5， total 12964 prve next

3. The search engine also allows the user to search for a specific virus subtype (e.g. A/Anhui/1/2005); the search engine and the database will then find all the sequences, publications, patents, clinical trial files and regulatory approval files that mention that subtype.

Example 2. Search results for subtype: A/Anhui/1/2005 in "Basic Search"

IVTM identifiers of : A/Anhui/1/2005

Original Specimen numbers	IVTM-ORG205
Date of collection	2005
Specimen Type	virus isolate egg
Place of collection	China
IVTM Parent	IVTM-SRC91
Influenza type	A/H5N1

(a) Nucleotide sequences

Order	Definition	accession1	GI	Year	Length	Link
1	Influenza A virus (A/Anhui/1/2005(H5N1))	null	null	null	2280	NCBI Openflu
2	Influenza A virus (A/Anhui/1/2005(H5N1)) segment 6 neuraminidase (NA) gene, complete cds	EU128239	156763808	2007	1350	NCBI Openflu
3	Sequence 76 from Patent WO2009020236	GN059867	224763482		1704	NCBI Openflu
4	Influenza A virus (A/Anhui/1/2005(H5N1)) segment 7 sequence	CY060170	293601637	2010	859	NCBI Openflu
5	Influenza A virus (A/Anhui/1/2005(H5N1)) segment 4 hemagglutinin (HA) gene, complete cds	HM172104	295915620	2010	1704	NCBI Openflu

1 to 5， total 26 prve next

(b) Publications

Order	Paper Title	Journal	Year	Link
1	Reliability of pseudotyped influenza viral particles in neutralizing antibody detection.	PLoS ONE	2014	PubMed
2	Inhibitory activities of 3-trifluoromethyl benzamide derivatives against the entry of H5N1 influenza viruses	Nan Fang Yi Ke Da Xue Xue Bao	2014	PubMed
3	A Replicating Modified Vaccinia Tiantan Strain Expressing an Avian-Derived Influenza H5N1 Hemagglutinin Induce Broadly Neutralizing Antibodies and Cross-Clade Protective Immunity in Mice.	PLoS ONE	2013	PubMed
4	A single residue substitution in the receptor-binding domain of H5N1 hemagglutinin is critical for packaging into pseudotyped lentiviral particles.	PLoS ONE	2012	PubMed
5	Homologous and heterologous antibody responses to a one-year booster dose of an MF59 (Â®) adjuvanted A/H5N1 pre-pandemic influenza vaccine in pediatric subjects.	Hum Vaccin Immunother	2012	PubMed

1 to 5， total 29 prve next

(c) Patents

Order	Patent number	Patent title	Application date	Publication date	Link
1	WO/2011/136738	(EN) UNIVERSAL VACCINE AGAINST H5N1 LINEAGES (FR) VACCIN UNIVERSEL CONTRE LES LIGNÃES H5N1	2011-02-09	2011-11-03	WIPO
2	WO/2014/099931	(EN) INFLUENZA VIRUS VACCINES AND USES THEREOF (FR) VACCINS CONTRE LE VIRUS DE LA GRIPPE ET LEURS UTILISATIONS	2013-12-17	2014-06-26	WIPO
3	WO/2009/092038	(EN) INFLUENZA DNA VACCINATION AND METHODS OF USE THEREOF (FR) VACCINATION A BASE D'ADN DE LA GRIPPE ET METHODES D'UTILISATION ASSOCIEES	2009-01-16	2009-07-23	WIPO
4	WO/2011/141658	(EN) PEPTIDES WITH ANTIPROTEASE ACTIVITY (FR) PEPTIDES A ACTIVITE ANTIPROTEASIQUE	2011-04-21	2011-11-17	WIPO
5	WO/2009/132195	(EN) IMMORTAL AVIAN CELL LINE AND METHODS OF USE (FR) LIGNÃE CELLULAIRE AVIAIRE IMMORTELLE ET PROCÃDÃS DâUTILISATION	2009-04-23	2009-10-29	WIPO

1 to 5， total 33 prve next

(d) Clinical trials

Other	Public title	Status	Phase	Year	Study type	Country	Link
1	Studies on effectiveness and safety of vaccination with H5N1 prepandemic vaccines, and cross-immunity among H5N1 viruses	Recruiting	Not applicable	2016	Interventional	Japan	International Clinical Trials Registry Platform
2	Immunogenicity of Monovalent Inactivated Influenza A/H7N9 Virus Vaccine.	Recruiting	Phase 2	2016	Interventional	United States	International Clinical Trials Registry Platform
3	Efficacy and safety of the avian influenza A/H7N9 inactivated whole-virus vaccine produced using the embryonated egg in human (Investigator-initiated Phase 2b trial)	Recruiting	Phase II	2016	Interventional	Japan	International Clinical Trials Registry Platform
4	A Study to Evaluate Safety, Immunogenicity, and Lot-to-Lot Consistency of H5N1 Subunit Influenza Virus Vaccine in Healthy Adult Subjects =18 Years of Age	Active, not recruiting	Phase 3	2016	Interventional	United States	International Clinical Trials Registry Platform
5	Safety and Immunogenicity of IVACFLU-A/H5N1 in Vietnamese Adult	Recruiting	Phase 2	2016	Interventional	Vietnam	International Clinical Trials Registry Platform

1 to 5， total 244 prve next

4. Within each list of search results, each result can be clicked for further information. Thus, for instance, if the user clicks on the first result under "**Publications"** in **Example 1(c)** above, a new page will open containing more information on the publication, including a link to the paper (see Example 3 below).

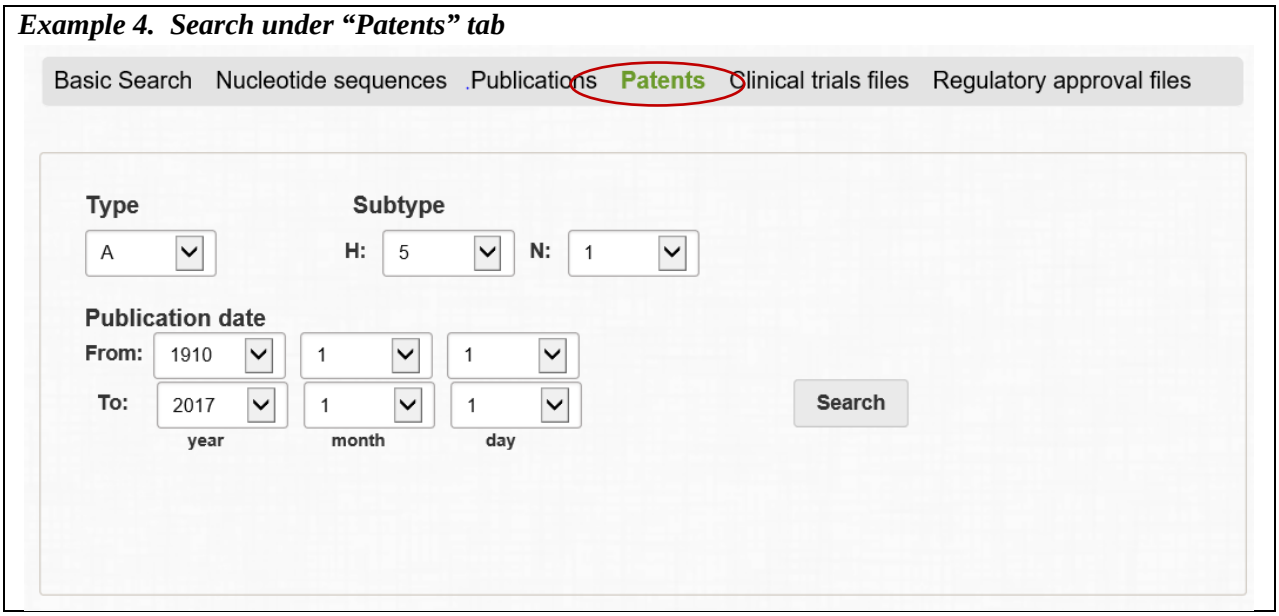
Example 3. Using a search result (refer to Example 2(b) above)

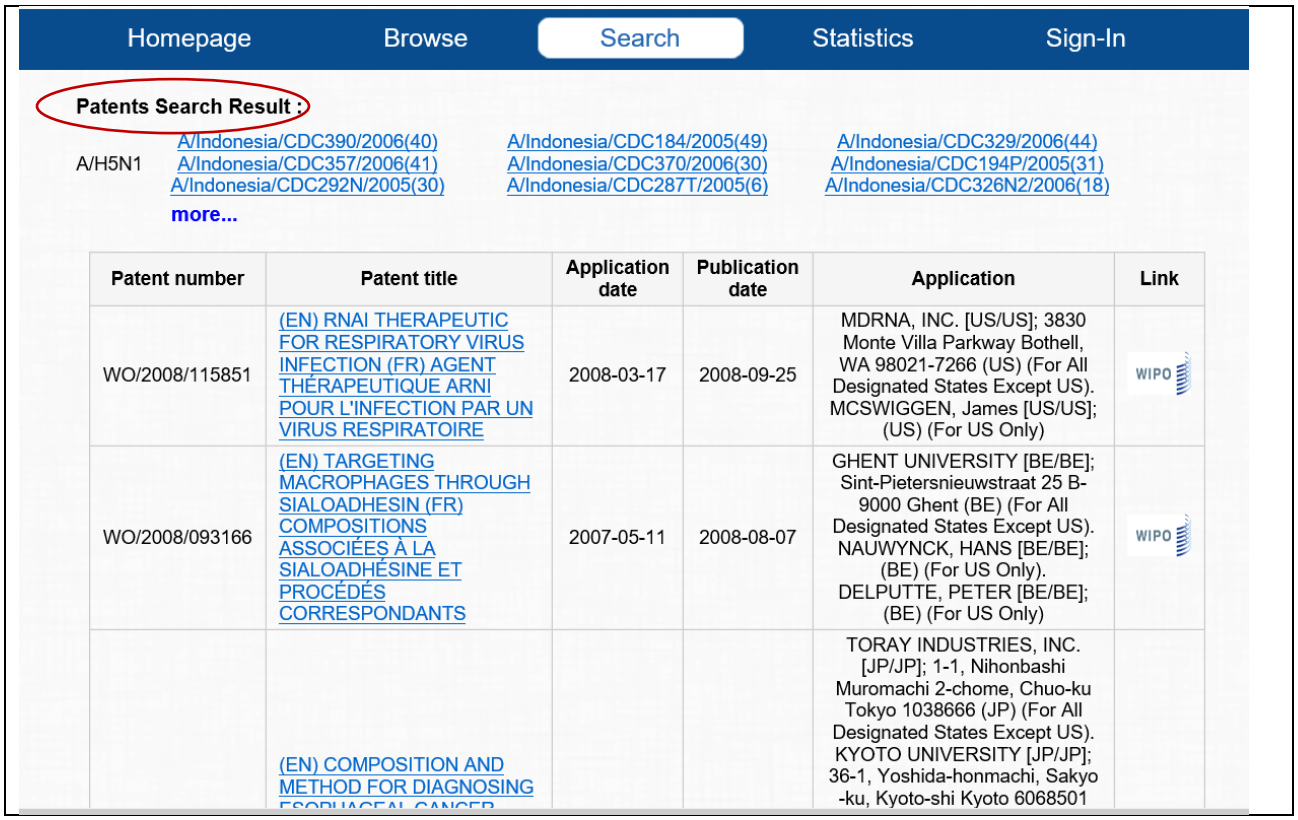
Paper information	Paper Title	Reliability of pseudotyped influenza viral particles in neutralizing antibody detection.
	Journal	PLoS ONE
	Authors	Yang Jinghui J Institute of Medical Biology, Chinese Academy of Medical Sciences & Peking Union Medical College, Kunming, Yunnan, China. Li Weidong W Institute of Medical Biology, Chinese Academy of Medical Sciences & Peking Union Medical College, Kunming, Yunnan, China. Long Yunfeng Y Institute of Medical Biology, Chinese Academy of Medical Sciences & Peking Union Medical College, Kunming, Yunnan, China. Song Shaohui S Institute of Medical Biology, Chinese Academy of Medical Sciences & Peking Union Medical College, Kunming, Yunnan, China. Liu Jing J Institute of Medical Biology, Chinese Academy of Medical Sciences & Peking Union Medical College, Kunming, Yunnan, China. Zhang Xinwen X Institute of Medical Biology, Chinese Academy of Medical Sciences & Peking Union Medical College, Kunming, Yunnan, China. Wang Xiaoguang X Minhang District Center for Disease Control and Prevention, Shanghai, China. Jiang Shude S Institute of Medical Biology, Chinese Academy of Medical Sciences & Peking Union Medical College, Kunming, Yunnan, China. Liao Guoyang G Institute of Medical Biology, Chinese Academy of Medical Sciences & Peking Union Medical College, Kunming, Yunnan, China.
	Author Information	Institute of Medical Biology, Chinese Academy of Medical Sciences & Peking Union Medical College, Kunming, Yunnan, China.
	Doi	10.1371/journal.pone.0113629
	Volume	9
	Issue	12

Publishing information	Pubtype	Journal Article
	Issn	
	Eissn	1932-6203
	Pubdate	2014
	Country	United States
	Language	eng
	PubMed ID	25436460
Abstract	Abstract	Current influenza control strategies require an active surveillance system. Pseudotyped viral particles (pp) together with the evaluation of pre-existing immunity in a population might satisfy this requirement. However, the reliability of using pp in neutralizing antibody (nAb) detection are undefined.
Link PubMed		

5. In addition to the "**Basic Search**" tab, more advanced searches can be conducted for a virus or virus subtype name using the other tabs. In the example below, a search for A/H5N1 was conducted using only the "**Patents"** tab.

Example 4. Search under "Patents" tab





Homepage Browse Search Statistics Sign-In

Patents Search Result :

A/H5N1 A/Indonesia/CDC390/2006(40) A/Indonesia/CDC357/2006(41) A/Indonesia/CDC292N/2005(30) A/Indonesia/CDC184/2005(49) A/Indonesia/CDC370/2006(30) A/Indonesia/CDC287T/2005(6) A/Indonesia/CDC329/2006(44) A/Indonesia/CDC194P/2005(31) A/Indonesia/CDC326N2/2006(18)

more...

Patent number	Patent title	Application date	Publication date	Application	Link
WO/2008/115851	(EN) RNAI THERAPEUTIC FOR RESPIRATORY VIRUS INFECTION (FR) AGENT THÉRAPEUTIQUE ARNI POUR L'INFECTION PAR UN VIRUS RESPIRATOIRE	2008-03-17	2008-09-25	MDRNA, INC. [US/US]; 3830 Monte Villa Parkway Bothell, WA 98021-7266 (US) (For All Designated States Except US). MCSWIGGEN, James [US/US]; (US) (For US Only)	WIPO
WO/2008/093166	(EN) TARGETING MACROPHAGES THROUGH SIALOADHESIN (FR) COMPOSITIONS ASSOCIÉES À LA SIALOADHÉSINE ET PROCÉDÉS CORRESPONDANTS	2007-05-11	2008-08-07	GHENT UNIVERSITY [BE/BE]; Sint-Pietersnieuwstraat 25 B-9000 Ghent (BE) (For All Designated States Except US). NAUWYNCK, HANS [BE/BE]; (BE) (For US Only). DELPUTTE, PETER [BE/BE]; (BE) (For US Only)	WIPO
	(EN) COMPOSITION AND METHOD FOR DIAGNOSING ESOPHAGEAL CANCER			TORAY INDUSTRIES, INC. [JP/JP]; 1-1, Nihonbashi Muromachi 2-chome, Chuo-ku Tokyo 1038666 (JP) (For All Designated States Except US). KYOTO UNIVERSITY [JP/JP]; 36-1, Yoshida-honmachi, Sakyo -ku, Kyoto-shi Kyoto 6068501	

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