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## Viral Host Range database, an online tool for recording, analyzing and disseminating virus-host interactions

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1 **Title**

2 Viral Host Range database, an online tool for recording, analyzing and disseminating virus-  
3 host interactions

4

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19

## 20 **Abstract**

### 21 **Motivation**

22 Viruses are ubiquitous in the living world, and their ability to infect more than one host  
23 defines their host range. However, information about which virus infects which host, and  
24 about which host is infected by which virus, is not readily available.

### 25 **Results**

26 We developed a web-based tool called the Viral Host Range database to record, analyze and  
27 disseminate experimental host range data for viruses infecting archaea, bacteria and  
28 eukaryotes.

### 29 **Availability and implementation**

30 The ViralHostRangeDB application is available from <https://viralhostrangedb.pasteur.cloud>.  
31 Its source code is freely available from the Gitlab hub of Institut Pasteur  
32 (<https://gitlab.pasteur.fr/hub/viralhostrangedb>).

33

### 34 **Introduction**

35 Viral genomic data is expanding, and their *in silico* analysis poses many challenges, including  
36 how to predict the likely host of a given virus (de Jonge, et al., 2020; Dzunkova, et al., 2019;  
37 Kieft, et al., 2020; Li, et al., 2020; Santiago-Rodriguez and Hollister, 2019). The gold standard  
38 for host identification remains the experimental evidence, which can take a long time and  
39 considerable effort to obtain. Four years passed between the prediction of *Bacteroidetes* as  
40 the putative host for crAssphage (the most abundant human gut bacteriophage) and the first  
41 experimental evidence that the strain *Bacteroidetes intestinalis* APC919/174 serves as a host  
42 for  $\phi$ crAss001 (Dutilh, et al., 2014; Shkoporov, et al., 2018).

43 The GenBank (Sayers, et al., 2019) database might be expected to provide information about  
44 the host of a virus, but these records mostly identify the host only to genus or species level,  
45 which is insufficient. For instance, the host indicated for bacteriophage T4 is the bacterium  
46 *Escherichia coli*, with no identification of a strain, which is as imprecise as indicating that  
47 human cells are the host for HIV-1. For a non-expert, such information suggests that any *E.*

48 *coli* strain can be infected by bacteriophage T4, or that any human cell can be infected by  
49 HIV-1. Another public resource that could be used is the International Committee on  
50 Taxonomy of Viruses (ICTV) (Lefkowitz, et al., 2018). However, host is not indicated in the  
51 data available from the ICTV website ([talk.ictvonline.org](http://talk.ictvonline.org)). Finally, it is possible to search in  
52 microbial collections (ATCC; [www.atcc.org](http://www.atcc.org), DSMZ; [www.dsmz.de](http://www.dsmz.de)) the host associated with a  
53 deposited virus, but, unfortunately, these resources contain data for only limited numbers of  
54 published virus/host pairs.

55 Over and above the identification of a single host for virus propagation, virus host range is  
56 another characteristic that is not readily available from public data sources. For viruses  
57 infecting multicellular organisms, including humans, in particular, the determination of host  
58 range is limited by the ability to grow cell lines. By contrast, for unicellular organisms, the  
59 number of hosts to be tested is very large, but unfortunately data is rarely published under  
60 an exploitable format. Interestingly, bacteriophage host range data is as old as the first  
61 article naming these viruses, published in 1917 by F. d'Herelle, in which bacteriophages  
62 infecting a *Shiga* strain were reported to be unable to infect *Flexner* or *Hiss* strains  
63 (d'Herelle, 1917).

64 For decades, viral host range tests were routinely performed for the typing of bacteria  
65 (Sabat, et al., 2013; Sechter, et al., 2000). Nowadays, host ranges are being determined for  
66 an increasing number of bacteriophages to identify candidates for phage therapy. This  
67 treatment for bacterial infections was originally proposed in 1917, and is used regularly in  
68 some countries (Georgia, Poland) (d'Herelle, 1917; Kutateladze, 2015). Its use is now  
69 expanding worldwide to treat infections caused by antibiotic-resistant pathogens  
70 (Corbellino, et al., 2019; Dedrick, et al., 2019; Jennes, et al., 2017; Schooley, et al., 2017).  
71 Consequently, semi-automated systems for high-throughput host range tests have been  
72 developed (<http://www.aphage.com/the-science/>). However, only the small number of  
73 positive outputs from these tests are finally used, with the bulk of the information obtained  
74 discarded and, thus, unavailable.

75 Another major challenge is the integration of host range data into a single searchable and  
76 analysis tool. Viral host range data is, by definition, a variable, which should be regenerated  
77 dynamically following the acquisition of new data.

78

## 79 **Results**

80 We circumvented the challenges associated with virus host range analysis, by designing the  
81 Viral Host Range database (VHRdb, <https://viralhostrangedb.pasteur.cloud/>), which compiles  
82 experimental host range data provided by contributors. This open web-based resource can  
83 be used to explore and analyze publicly accessible data with a powerful search engine that  
84 scans data and metadata (virus or host names, contributor name, location, GenBank  
85 accession number, etc.). Not only can users find a virus, but they can also immediately  
86 identify the set of hosts on which it has been tested, across all the available data. Filters,  
87 analysis and display settings can facilitate rapid visualization of the most relevant  
88 information, such as the highest host range score or the most susceptible host (Figure 1).  
89 Importantly, when discrepancies between datasets are detected, they are highlighted and  
90 direct access is provided to the source data, for further investigations.

91 We designed a user-guided process for uploading data compatible with the VHRdb mapping  
92 tool, to facilitate comparisons of datasets. This mapping tool is the cornerstone of VHRdb,  
93 translating the contributor's original (numerical) data into a unified ranking system. The  
94 mapping tool was designed to allow each contributor to classify the results of virus-host  
95 interaction tests into a maximum of three responses: "0", for "no infection"; "2" for  
96 "infection"; and "1" for "intermediate", corresponding to any interaction that is different  
97 from "0" and "2". Then, contributors can readily compare their results with publicly available  
98 datasets (curated by administrators to ensure that the database remains homogeneous). If  
99 kept private, data are neither accessible to, nor curated by administrators. Analysis across a  
100 restricted number of datasets is also possible, to focus on specificities associated with one or  
101 several viruses or hosts.

102 Another issue affecting the accurate appreciation of a virus host range is the lack of precise  
103 characterizations of tested hosts. In particular, most of clinical isolates used to determine  
104 the host range of bacteriophages for phage therapy applications are not sequenced.. In  
105 addition, viruses themselves evolve over time and adapt their host range to the available  
106 hosts (Rothenburg and Brennan, 2020).. The VHRdb therefore handles GenBank accession  
107 numbers for both viruses and hosts, as a solution to provide unique identifiers.

108 In addition to the identification of suitable hosts for viruses and the cross-analysis of  
109 experimental tests, we anticipate that the VHRdb will become a resource for the  
110 development of machine learning approaches, which require large amounts of data, to  
111 improve the prediction of the host of a virus, or even the receptor that it uses (Leite, et al.,  
112 2018; Young, et al., 2020). It could also be used more directly by clinicians, who will  
113 increasingly have access to the genome sequences of pathogens. If the strain infecting a  
114 patient is closely related to a tested strain present in the VHRdb, candidate bacteriophages  
115 are immediately identified, shortening the time required to develop an appropriate  
116 treatment. The VHRdb will also provide opportunities to address fundamental questions in  
117 virology, from ecological dynamics to the molecular mechanisms underlying virus-host  
118 interactions.

119 The VHRdb is a unique, publicly accessible resource for the community of microbial  
120 virologists, for the rapid identification, characterization and dissemination of data for virus-  
121 host interactions of broad interest to the educational, scientific and medical communities,  
122 and to private sector entities developing applications.

123 At the time of publication, the VHRdb holds 15,753 interactions obtained from 739 viruses  
124 infecting 1,664 archaeal, bacterial or protist hosts, including the entire Felix d'Herelle  
125 collection of bacteriophages.

## 126 **Methods**

### 127 **Data Availability**

128 The ViralHostRangeDB application is available from <https://viralhostrangedb.pasteur.cloud>.  
129 Its source code is freely available from the Gitlab hub of Institut Pasteur  
130 (<https://gitlab.pasteur.fr/hub/viralhostrangedb>), under the terms of the MIT license,  
131 together with detailed documentation (<https://hub.pages.pasteur.fr/viralhostrangedb/>)  
132 including instructions for use, deployment and administration purposes. A demonstration  
133 server can be run directly from a docker image  
134 (<https://hub.docker.com/r/viralhostrangedb/demo>), providing a way of testing all features  
135 of the application, including the privileges and (in)visibility of private data sources.

### 136 **Architecture**

137 The architecture of the ViralHostRangeDB web application is based on the Django Web  
138 Framework, and the PostgreSQL database. Data are displayed, on the server side, in the  
139 Django REST framework. This environment provides efficient and safe data storage as well as  
140 tight control access. The application, its database and routine processes (backup, email  
141 notifications, virus/host identifier analysis, etc.), are hosted on a Kubernetes cluster  
142 (<https://kubernetes.io/>), providing high availability, scalability and fail-over. The global  
143 software quality of the application is ensured through unit test scenarios covering 99% of  
144 the code base.

### 145 **Importing data**

146 Any authenticated user can contribute datasets via the top menu. Datasets can be uploaded  
147 as Excel files as detailed in the online documentation  
148 ([https://hub.pages.pasteur.fr/viralhostrangedb/compatible\\_file.html](https://hub.pages.pasteur.fr/viralhostrangedb/compatible_file.html)). Excel data files are  
149 imported with the Pandas and xlrd Python packages (McKinney, 2017). During the mapping  
150 of the responses of a file onto the global scheme, the thresholds suggested to users are  
151 calculated with the NumPy (Oliphant, 2006) and Scikit-learn (Pedregosa, et al., 2011)  
152 packages. The NCBI identifiers describing the host and virus strains are validated with Entrez  
153 web services (Sayers, et al., 2020) which are queried with the BioPython (Cock, et al., 2009)  
154 package.

### 155 **Privacy**

156 The access to uploaded datasets can be finely controlled, by restricting it to the uploader  
157 only, sharing it with a specific set of other users, or making it public. It is also possible to set  
158 permissions for the edition of a dataset for each user. Private data sources can be accessed  
159 only by explicitly authorized users, regardless of whether the user is a curator or a privileged  
160 administrator. To secure edition operations on the datasets, all modifications are logged and  
161 stored in histories, to allow rollback.

### 162 **Search tool**

163 The web interface allows the interrogation of datasets. A `search module`, accessible either  
164 through a quick search box or through a specific advanced search page, can be used to  
165 discover datasets through full text and specific filters (e.g. Host or Virus names, contributor,  
166 publication...). The exploration module, accessible from the top menu or from the search

167 results, provides the main functionality of the application: the ability to compare the  
168 responses of any number of hosts to any number of viruses, across all the datasets  
169 accessible.

170



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178

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233

234

235 **Legend to Figure 1.** Diagram presenting the main functionalities of the Viral Host Range  
236 database. The top panel (Search) introduces the search tool and links to subsequent  
237 information. The bottom panel (Contribute) presents the main steps that contributors must  
238 achieve to record new data. Shown in the middle panel (Explore) is an example of results  
239 obtained from dataset comparison, using the datasets selected from the searched results  
240 displayed in the top panel and the newly contributed data displayed in the bottom panel  
241 (red arrows). Main tools and options to select, rank and display data are also indicated.

242



### Search

Enter any term: viruses, hosts, contributors, etc...

**Search results for T4**

**Virus**  
T4 (NC\_000866.4) HER 27

**Host**  
Patient 1 Clone 1

**Data Source**  
E. coli phages T4 subgroups against EPEC and ETEC strains (From LAMY-BESNIER Query) Created on: 2020-04-23; Last edited: 2020-09-11

**Filter search results**

**Virus T4** (NCBI NC\_000866.4) **HER 27**

Data source: E. coli phages T4 subgroups against EPEC and ETEC; Félix D'Hérelle collection of bacterial strains

Host	Response
Escherichia coli B	0
(EPEC) E. coli O111:K58	0
(EPEC) E. coli O112:K66	0
(EPEC) E. coli O124:K72	0
(EPEC) E. coli O125:K70	0
(EPEC) E. coli O15:H51	0
(EPEC) E. coli K12	2

### Explore

**Selection**

Search

- ALS05\_P1, ALS05\_P2, ALS05\_P3 test on the ECOR collection
- Chloroviruses
- CLB\_P1, CLB\_P2, CLB\_P3 test on the ECOR collection
- E. coli phages from D'Hérelle collection against E. coli isolates from infant fecal samples
- E. coli phages T4 subgroups against EPEC and ETEC strains
- E. coli strain M181 phages test on the ECOR collection and other strains
- Félix D'Hérelle collection of bacterial viruses

**Analysis Tools (2)** Data filtering Rendering (1)

- Show the infection ratio for viruses
- Show the infection ratio for hosts
- Consider all positive responses as an infection

**Virus T4**, **Host E. coli O125:K70**

Data source name	Response
E. coli phages T4 subgroups against EPEC and ETEC strains	0
My_new_data_source	1

**Data source**: E. coli phages T4 subgroups against EP... **Virus**: All relevant viruses\* **Host**: All relevant hosts\*

Legend: 0: No infection 1: Intermediate 2: Infection

Host	(HGT38887) E. coli K12	(EPEC) E. coli O125:K70	(EPEC) E. coli O111:K58	(EPEC) E. coli O124:K72	(EPEC) E. coli O112:K66	(EPEC) E. coli O15:H51	E. coli 2
<b>Virus</b> JF	85%	29%	14%	14%	8%	8%	8%
(NC_000866.4) HER:27) T4	2	0-1	0	0	0	0	0
(NC_04928) RB69	2	0	0	0	0	0	0
(NC_005068) RB49	2	2	0	2	0	0	0
(EU863408) JSE	2	0	0	0	0	0	0
(NC_012741) JS98	2	0	0	0	0	0	0
(EU863409) JS10	2	0	2	0	0	0	0
(NC_001604.1) T7		2					1

Ranking (optional)  
Infection ratio

Comparing data sources

### Contribute

**Step 1. Fill metadata**

Name\*  
My\_new\_data\_source

Name of the data source

Public  
Is the data source publicly readable? Otherwise you can allow specific users.

Life domain\*  
Bacteria

Description  
Host range test performed on the d/mly by X.Y (spotting serial dilution on plates).

**Step 2. Upload Excel file**

	A	B	C
1		E. coli O125:K70	E. coli 2
2	T4 (NC_000866.4)	1	0
3	T7 (NC_001604.1)	3	2

**Step 3. Mapping scheme**

Global mapping: No infection < 1,25 ≤ Intermediate < 2,5 ≤ Infection

Raw responses: 0, 1 → 2 → 3