Ebola virus:

Developing a life-saving antibody therapy with public DSI

An unprecedented outbreak of a deadly virus

The 2013-16 Ebola epidemic in West Africa was the worst outbreak in the history of the disease. It ultimately led to thousands of deaths and tens of thousands of cases across ten countries (with Guinea, Liberia, and Sierra Leone seeing widespread transmission of the disease) (fig 1). The scope of this outbreak was (and remains) unprecedented both in terms of the number of people infected and the geographic spread of the virus, largely due to it reaching densely populated urban areas for the first time (numerous cases were reported in the capitals of the three worst affected West African countries, all cities of over a million people)[1].

Ebola virus disease is often fatal, with the World Health Organization estimating that around half of cases end in death (although case fatality rates have varied between 25% and 90% in past outbreaks). Ebola is normally rare, so populations in areas at risk are immunologically naïve, meaning their immune system has not developed antibodies to the virus through exposure. This makes them vulnerable to severe infections. At the time of the 2013-16 outbreak, no approved clinical therapies or vaccines were available to treat or prevent Ebola infection[2].

[1] CDC. *2014-2016 Ebola Outbreak in West Africa.* 2019. https://www.cdc.gov/vhf/ebola/history/2014-2016-outbreak/index.html#print Accessed on 16/02/2023

[2] Pascal KE, Dudgeon D, Trefry JC, Anantpadma M, Sakurai Y, Murin CD, Turner HL, Fairhurst J, Torres M, Rafique A, Yan Y, Badithe A, Yu K, Potocky T, Bixler SL, Chance TB, Pratt WD, Rossi FD, Shamblin JD, Wollen SE, Zelko JM, Carrion R Jr, Worwa G, Staples HM, Burakov D, Babb R, Chen G, Martin J, Huang TT, Erlandson K, Willis MS, Armstrong K, Dreier TM, Ward AB, Davey RA, Pitt MLM, Lipsich L, Mason P, Olson W, Stahl N, Kyratsous CA. *Development of Clinical-Stage Human Monoclonal Antibodies That Treat Advanced Ebola Virus Disease in Nonhuman Primates.* Journal of Infectious Diseases. 2018 Nov 22;218(suppl_5)

Using DSI to develop the first treatment and prevention drugs

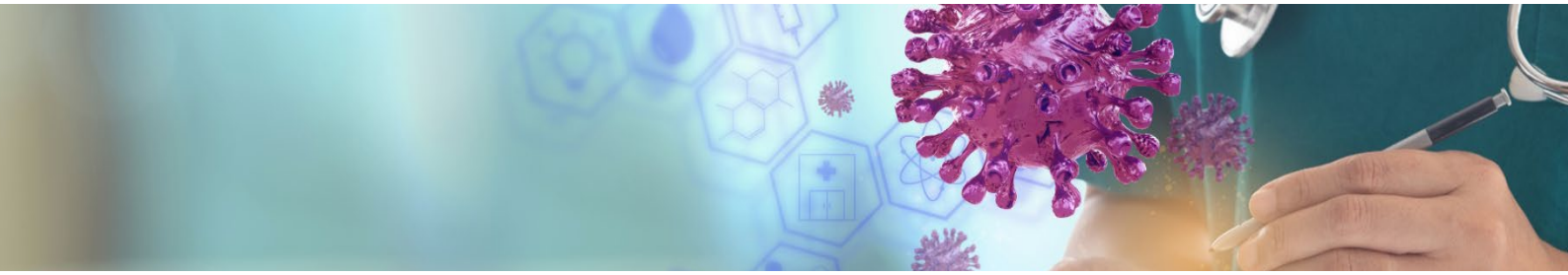
The scale of the 2013-16 outbreak spurred greater interest into Ebola treatment research, with the first vaccines and monoclonal antibody therapies being approved in 2019 and 2020. The first Ebola antibody therapy to be approved in the United States was a drug called Inmazeb, created and sold by Regeneron Pharmaceuticals. The process of developing Inmazeb was the work of several years, and relied on the use of Ebola DSI that was available in public databases, including samples collected during the 2013-16 outbreak in West African countries. The drug was shown to prevent deaths from Ebola during a later outbreak in the Democratic Republic of Congo[3].

On the surface, it is a story of a company using a single sequence sourced from African genetic resources to develop a commercial antibody therapy to Ebola, without any requirement for benefit sharing (the Nagoya Protocol was not in place when the sample was collected and the sequence uploaded in the open access database). However, looking a bit deeper, it becomes clear that this story is about more than just one individual sequence.

Even though the C15 Ebola genome sequence was referenced in the Regeneron patent (*human antibodies to Ebola virus glycoprotein*, 2016[4]) (fig 2), it does not claim any novelty regarding the Ebola sequence. It merely describes a method for generating therapeutic antibodies against the Ebola glycoprotein. By the end of 2014, there were already several hundred Ebola virus sequences available in public databases. Thus, Regeneron had access to many nearly identical DSI samples from different source countries, including many other whole genomes from samples from the ongoing outbreak. A different Ebola sequence could equally be used and listed in the patent, which would have generated a similar or identical glycoprotein. If overly complex mechanisms for benefit sharing that involve bilateral elements are implemented, users could avoid regulated DSI and use non-regulated DSI, resulting in jurisdiction shopping.

[3] Mulangu S, Dodd LE, Davey RT Jr, Tshiani Mbaya O, Proschan M, Mukadi D, Lusakibanza Manzo M, Nzolo D, Tshomba Oloma A, Ibanda A, Ali R, Coulibaly S, Levine AC, Grais R, Diaz J, Lane HC, Muyembe-Tamfum JJ; PALM Writing Group; Sivahera B, Camara M, Kojan R, Walker R, Dighero-Kemp B, Cao H, Mukumbayi P, Mbala-Kingebeni P, Ahuka S, Albert S, Bonnett T, Crozier I, Duvenhage M, Proffitt C, Teitelbaum M, Moench T, Aboulhab J, Barrett K, Cahill K, Cone K, Eckes R, Hensley L, Herpin B, Higgs E, Ledgerwood J, Pierson J, Smolskis M, Sow Y, Tierney J, Sivapalasingam S, Holman W, Gettinger N, Vallée D, Nordwall J; PALM Consortium Study Team. *A Randomized, Controlled Trial of Ebola Virus Disease Therapeutics.* New England Journal of Medicine. 2019 Dec 12;381(24)

[4] Regeneron Pharmaceuticals inc. *Human antibodies to ebola virus glycoprotein.* WO 2016/123019 A1 World Intellectual Property Organisation. 2016. https://patentimages.storage.googleapis.com/a6/60/a4/c4ae44025f87d6/WO2016123019A1.pdf



Access and benefit-sharing when publicly available DSI is used for commercial ends

In December 2022, the Parties to the CBD agreed that the benefits from the use of DSI should be shared fairly and equitably. For instance, the commercialization of a product developed by a biotechnology company using DSI from public databases should trigger monetary benefit sharing. However, it is crucial that the policies and mechanisms through which this benefit-sharing takes place are designed to be simple and effective. Tracking and tracing the use of every individual sequence is not practical. Similarly, it is essential that benefit-sharing obligations cannot be avoided and that benefits flow back to affected regions.

At the same time, any attempt to restrict or disincentivize sharing of DSI risks undermining potentially life-saving research. As this patent was being filed, complex scientific work was underway simultaneously in multiple labs. The large set of sequences available to researchers, from the current outbreak and past outbreaks, enabled scientists to understand how the virus was evolving and spreading. The value of DSI for scientists increases in proportion to how much is available to them.

Key takeaways

Open access to DSI provides non-monetary benefits by enabling rapid actions and development of important public health responses, like diagnosis methods, medical treatments, epidemiological monitoring or vaccines. The **trigger point for benefit sharing should not be at the level of individual sequences nor at the public databases** (subscription models, paywalls). On the other hand, commercialization of products could be a trigger point for monetary benefit sharing (e.g. patent royalties, levies, percentage of the revenue from sales or retail).

The multilateral system for benefit sharing must be **compatible with the scientific process.** In practice, DSI users work with the global dataset and not just a few sequences from one country. The multilateral benefit sharing system should make it easy for users to continue working with this global dataset and not hinder research and development that contributes to global health and other fields.

It is necessary to have a **single, global and predictable set of rules** for benefit sharing from DSI. Bilateral exceptions to the multilateral mechanism will add complexity, incompatibility, and avoidance behaviour, resulting in jurisdiction shopping.

Any mechanism that disincentivizes sharing of DSI risks undermining potentially life-saving research.

Fig 1. *Map of Guinea showing the initial locations of the 2013-16 Ebola outbreak (in red).*[5]

[5] Baize, S., Pannetier, D., Oestereich, L., Rieger, T., Koivogui, L., Magassouba, N., Soropogui, B., Sow, M. S., Keïta, S., De Clerck, H., Tiffany, A., Dominguez, G., Loua, M., Traoré, A., Kolié, M., Malano, E. R., Heleze, E., Bocquin, A., Mély, S., … Günther, S. (2014). Emergence of Zaire Ebola Virus Disease in Guinea. In New England Journal of Medicine (Vol. 371, Issue 15, pp. 1418–1425). Massachusetts Medical Society. https://doi.org/10.1056/nejmoa1404505

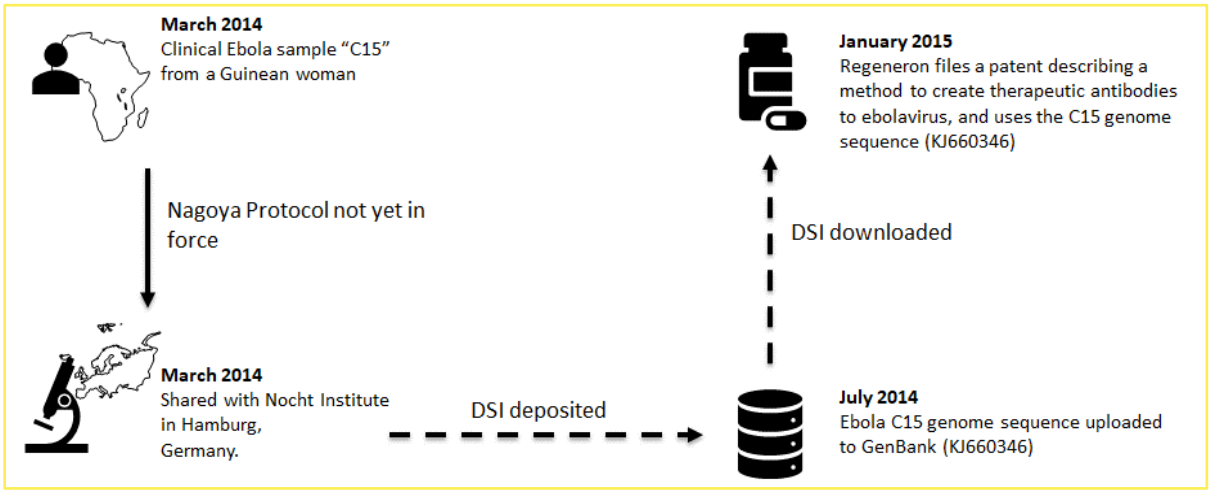


Fig 2. *Use of the Ebola C15 genome in patent for a life-saving antibody therapy.*
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