Michel Zaffran and colleagues (Jan 6, p 11)[1] assume that eradication will be achieved soon and focus on strategies to ensure that poliovirus will not be reintroduced into a polio-free world.[2]

The transition phase of polio eradication brings other challenges that are less obvious but equally demanding. Since 2000, polio eradication has been one of the best funded health programmes, consuming up to a fifth of WHO's budget.[3] Large amounts of this funding were voluntary contributions from WHO member states and non-governmental organisations, such as Rotary International. These resources supported polio vaccination, including immunisation programmes, and helped the introduction of infectious disease surveillance in at least 20 developing countries, mainly in Africa and the east Mediterranean (even when polio was prevalent in only three of them).[3]

Moreover, a third of WHO staff in the African Region receive salaries from the polio eradication budget; this staff comprises around 770 people, and 2730 contract workers also receive money from this budget.[4] It is unclear whether the voluntary funds will continue to be given when eradication has been achieved.[1] Even if these funds continue, it is unknown whether they will be channelled into the health sector.

Germany's substantial voluntary contributions towards polio eradication, for example, do not come from the Ministry of Health (who are otherwise responsible for contributions to WHO) but from the Ministry of Economic Cooperation and Development. It is conceivable that these funds will be earmarked in future for another purpose—eg, for education instead of health.

Planning for the so-called polio transition needs to move beyond measures to avoid reintroduction of the virus.[1,4,5] Strategies and funding mechanisms need to be developed to maintain WHO's experienced employee basis in Africa and the east Mediterranean and to maintain the routine immunisation services and disease surveillance systems that were co-funded by the polio eradication programme.

Here, two fundamental questions arise: is it a responsibility of WHO to keep routine national health systems functioning? Accepting this responsibility would be a paradigm shift. If so, should this responsibility be restricted only to countries that recently received polio funding, or to all countries with weak health systems? These two questions must be answered urgently; without clear answers, WHO might be forced to begin a programme to eradicate another pathogen, not because of a well considered and evidence-based decision but to raise the funds needed to keep essential elements of weak health systems operating.

We declare no competing interests.

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On the misuses of medical history

A surprising amount of bad history passes peer review in the sciences and medicine. What do we mean by bad history? One example would be the misuse of historical images. Many images of so-called plague used in scientific publications depict patients suffering from leprosy.[1] Another example is when commonly repeated claims about historical people or events are lifted from earlier scientific or medical writings, without checking whether professional historical scholarship has revised earlier interpretations. A medical article on vaginismus might dutifully repeat that the condition was first reported by a female medical writer, the so-called Trotula, in the 16th century, perpetuating a confusion debunked more than 30 years ago between an authorial fiction, Trotula, and an authentic 12th century healer named Trota. The passage always cited gives a remedy for a vaginal constrictive not, as is invariably implied, a disease entity.[2]

Scientific and biomedical authors seem compelled to include such historical references, but history is an active, dynamic field of enquiry, with methods not unlike those that drive science.

What can be done? First, we should recognise that the norm in history is that the consensus changes as new questions are asked and new sources uncovered. Citing a 1968 survey on the Justinianic Plague because it happens to arise in a PubMed search is not appropriate when excellent historical research on the pandemic has long since superseded that earlier work.[3]

No one now needs to be confined by the disciplinary firewalls that formerly kept disciplines unaware of what others were doing. We all have access to the riches of digital databases, but these too carry the risk of misinterpretation.[4] Although much good work is available online, it would be more valuable to find and talk to historians. Experts who specialise in the times and places under examination rarely feature in the peer review process for scientific or biomedical journals, and humanities scholars are rarely indexed by the major scientific and biomedical bibliographical

databases. The bulk of work that has been done on the Justinianic Plague in the past decade, for instance, does not appear in PubMed, SciVerse, or any other scientific database that we have consulted.

Authors and editors should be expected to invest the same amount of time on a literature review for historical questions as they do for the most recent consensus work in their own field. The payoff would be greater accuracy in historical claims and better science. As citations themselves become minable data, historical methods demand due acknowledgment.[5]

We declare no competing interests.

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C1 esterase inhibitor concentrates and attenuated androgens

Marc A Riedl and colleagues (July 25, 2017, p 1595)[1] conducted a phase 2, multicentre, randomised, double-blind, placebo-controlled cross-over trial in 32 patients to test the prophylactic efficacy of recombinant human C1 esterase inhibitor for hereditary angio-oedema. Once or twice weekly administration of recombinant human C1 esterase inhibitor (50 IU/kg) reached the primary endpoint (reduced number of attacks) in an intention-to-treat analysis.

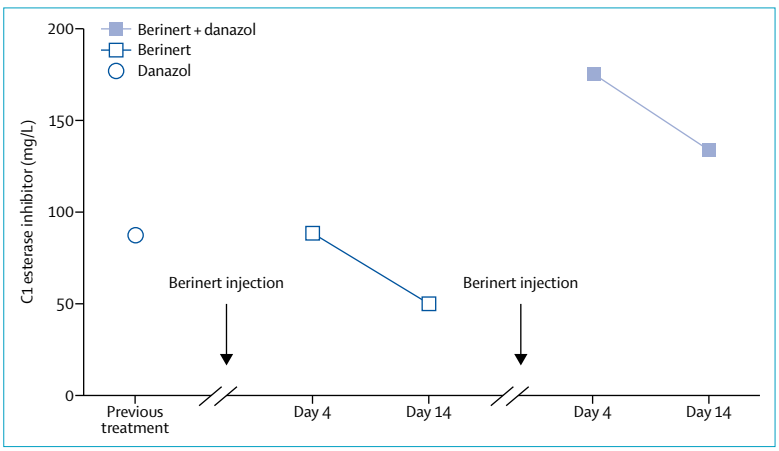

Figure: **Synergistic effect of C1 esterase inhibitor concentrates and attenuated androgens**
Plasma concentration of C1 esterase inhibitor 4 and 14 days after a single intravenous injection of human plasma-derived C1 esterase inhibitor concentrate (berinert, 1000 IU). Concentrations are without (white square) or with (blue square) concomitant attenuated androgen treatment (danazol, 400 mg/day). C1 esterase inhibitor concentration under attenuated androgen treatment (danazol, 200 mg/day) alone is shown as a white circle. This graph was created using data from our previous work.[2]

Notably, most of the study population had never received prophylactic treatment before study enrolment, although attenuated androgens or tranexamic acid were permitted per protocol. This situation suggests that patients under conventional prophylaxis did not meet the inclusion criteria of frequent attacks (ie, four or more per month for at least 3 consecutive months before study initiation).

Furthermore, we would like to emphasise the potential synergistic effect of recombinant human C1 esterase inhibitor and attenuated androgens for prophylaxis of hereditary angio-oedema as shown by the following case.[2] The patient was successfully treated for 26 years with attenuated androgens (danazol) until the age of 55 years when she developed new recurrent attacks. Danazol was switched to regular plasma-derived C1 esterase inhibitor (berinert) administered every 14 days, which was insufficient to prevent attacks—as shown by serial measurements of antigenic C1 esterase inhibitor levels. Clinical remission was achieved when danazol was reintroduced (figure).

Hereditary angio-oedema can be controlled by adequate substitution with C1 esterase inhibitor concentrates, as demonstrated by an inverse relationship between the relative risk of attack and functional C1 esterase inhibitor activity.[3] However, plasma-derived and recombinant C1 esterase inhibitors are very expensive, whereas attenuated androgens are affordable and efficient for prophylaxis of hereditary angio-oedema. Further studies should definitively analyse the potential synergistic effect between C1 esterase inhibitor concentrates and attenuated androgens. Cost-effectiveness of long-term prophylaxis of hereditary angio-oedema might be substantially improved as a result.

We declare no competing interests. YDM was supported by the Swiss National Research Fund (grant no. P300PB_174500).

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