Correspondence

Drug assessment in the Ebola virus disease epidemic in west Africa

In their Personal View, Simone Lanini and colleagues[1] argued that an adaptive randomised controlled trial (RCT) is the optimum solution to assess experimental therapeutics for Ebola virus disease and that non-RCTs are "profoundly unethical".

Lanini and colleagues distinguished study designs of experimental agents as randomised versus non-randomised studies, including within the latter anecdotal experiences and compassionate use. It is irrational to make no distinction between phase 2 clinical trials and compassionate treatment. Studies by our groups, which were also cited by Lanini and colleagues, are fully regulated phase 2 clinical trials with explicit study frameworks.

Moreover, we studied interventions that have been approved by regulatory authorities for use in man and implemented them only following full ethical review and approval. Clinical drug trials can be legitimately done only with the consent of individuals and communities. We worked with communities to facilitate open dialogue and partnership, which shows that RCTs would not have been accepted at the time the trials were initiated.

In 1990, recognising that traditional approaches to clinical trial processes were unnecessarily rigid and unsuitable for study of HIV treatments, Byar and colleagues[2] concluded, in their paper design considerations for AIDS trials, that non-RCTs could be considered in the following situations. First, "there must be sufficient experience to ensure that the patients not receiving therapy will have a uniformly poor prognosis". Second, "there must be no other treatment appropriate to use as a control". Third, "the therapy must not be expected to have substantial side effects". Fourth, "there must be a justifiable expectation that the potential benefit to the patient will be sufficiently large to make interpretation of a non-RCT unambiguous". Fifth, "the scientific rationale for the treatment must be sufficiently strong that a positive result would be widely accepted".

The Ebola epidemic clearly fulfils the first and second criteria, since the fatality is high.[3,4] The third criterion was met for most of the strategies studied. Regarding criterion four, our approach was to triage treatments into those with no effect that should be discarded quickly, from those with clear benefits that should be rolled out immediately, and those with promise that needs to be assessed in a RCT, in which combination antivirals could be also studied.[5] This strategy is also more acceptable to patients, physicians, and local communities.

A debate on clinical trial design during humanitarian crises is needed, but it has to be based on an accurate characterisation of the events and issues.

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Ebola: Europe–Africa research collaborations

No one would disagree with Giuseppe Ippolito and colleagues[1] about the need to strengthen Europe–Africa research collaborations for health threats such as Ebola. This imperative must, however, build upon the current landscape of partnerships for epidemic diseases research in Africa and elsewhere. The Europe–Africa clinical research response to Ebola has been impressive, and includes vaccine safety studies in west Africa,[2,3] the encouraging results of the ring vaccination trial in Guinea coordinated by WHO,[4] the first ever drug trial in Ebola undertaken by the favipiravir (JIKI) trial consortium (NCT02329054),[5] the RAPIDE consortium trials of brincidofovir (PACTR201411000939962) and TKM-130803 (PACTR201501000997429), and the Ebola-Tx (NCT02342171) and Ebola-CP (ISRCTN13990511) trials of convalescent plasma.

With the inclusion of diagnostic, virological, and anthropological research, Europe–Africa Ebola research collaborations have been prolific. These achievements, which should be celebrated, are partly the consequence of investments over the past 5 years in many of the areas highlighted by Ippolito and colleagues. To cite only a few, the International Severe Acute Respiratory and emerging Infections Consortium (ISARIC) has been striving to align existing networks since 2011, and has pioneered the development of pre-approved and adaptable

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syndrome-based protocols. ISARIC has African member networks and is active in building regional capacity and linkages. Affiliated with ISARIC, the European Union (EU)-funded Platform for European Preparedness Against (Re-)emerging Epidemics (PREPARE) is undertaking inter-epidemic syndrome-based studies across Europe, and both ISARIC and PREPARE have begun to address ethical, administrative, regulatory, and legal bottlenecks to rapid research. To accelerate and coordinate funding of a rapid research response to outbreaks, a network of funders has established the Global Research Collaboration for Infectious Disease Preparedness (GloPID-R). The European and Developing Countries Clinical Trials Partnership, funded by the EU, provides substantial support for training and capacity development in Africa in the conduct of clinical trials. At the European country level, initiatives such as REACTing (REsearch and ACTion targeting emerging infectious diseases) and The Global Health Network (TGHN) have emerged to support research preparedness and capacity within low-income and middle-income countries. TGHN is providing free web-based courses to deliver research skills training to researchers in low-resource settings, with more than 40 000 of these being taken online in Africa so far. These many successes and ongoing initiatives should be the platforms from which we continue to strengthen Europe–Africa partnerships and help empower African researchers and institutions.

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Preventing sepsis

As highlighted by Jonathan Cohen and colleagues in their Commission,[1] mortality remains high in severe forms of sepsis.[1] The authors provided an extensive review of the key issues to be addressed in future research to develop better treatment strategies that can improve the present scenario. In our view, in the absence of effective treatments, prevention of sepsis is the best way to diminish morbidity and mortality associated with this complication. Most patients with sepsis are elderly individuals with comorbidities.[2] Immunosenescence, cancer, and chronic treatment with steroids or immunosuppressors for respiratory or autoimmune diseases affect basal immune status, increasing the risk of infection and sepsis.[2] Critical illness or aggressive surgery represent an additional challenge for these patients because of the transient state of immunosuppression induced.

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Immunological assessment of these at-risk individuals (other than testing leukocyte counts in the blood) is not included in the routine exams they undergo in primary health centres or nursing homes. It is neither done when these patients are admitted to hospital or critical care units, nor when they are facing major surgery. Emergence of new technologies allows the status of both innate and adaptive immunity to be analysed at a reasonable cost. Examples of these technologies are assessment in the blood of the expression levels of selected immune-related genes, such as *HLA-DR*, by real-time PCR[3] or droplet digital PCR,[4] and quantification of interferons, cytokines, and chemokines with multiplex assays. These new tests could be complementary to conventional ones, such as quantification of CD4 and CD8 T-cell counts in the blood, quantification in serum of immunoglobulin isotypes and complement factors (C3, C4, B),[5] or the assessment of cellular immunocompetence by the QuantiFERON test.

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Intensification of hygienic measures, more careful monitoring of clinical signs of infection, implementation of earlier microbiological testing, prophylaxis with antibiotics, or delaying programmed surgery to allow immunological recovery in patients receiving immunosuppressors are all potential measures that could help to prevent community-acquired or nosocomial sepsis in predisposed patients because of their compromised immunological status. The potential role of drugs such as interleukin 15, interleukin 7, or IMT504 to restore immunity and prevent sepsis in these patients is an exciting field of

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