non-EU or EEA countries should be encouraged to apply this methodology for international comparability, and ultimately inform the development and implementation of prevention strategies.

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1 European Centre for Disease Prevention and Control. Point prevalence survey of healthcare-associated infections and antimicrobial use in European acute care hospitals. 2013. https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/healthcare-associated-infections-antimicrobial-use-PPS.pdf (accessed Oct 22, 2018).

2 Cassini A, Diaz Högberg L, Plachouras D, et al. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. *Lancet Infect Dis* 2018; published online Nov 5. http://dx.doi.org/10.1016/S1473-3099(18)30605-4.

3 Swissnoso. Point Prevalence Survey 2017 of healthcare-associated infections and antimicrobial use in Swiss acute care hospitals. 2018. www.swissnoso.ch/fileadmin/swissnoso/Dokumente/5_Forschung_und_Entwicklung/2_Punktpraevalenzstudie/ch_pps_2017_report_FINAL2.pdf (accessed Oct 19, 2018).

4 Colzani E, Cassini A, Lewandowski D, et al. A software tool for estimation of burden of infectious diseases in Europe using incidence-based disability adjusted life years. *PLoS One* 2017; **12:** e0170662.

The threat of bioterrorism

Manfred S Green and colleagues[1] reviewed the modern aspects of bioterrorism threats, using the US Centers for Disease Control and Prevention (CDC) classification for their analysis of biological agents with potential for bioterrorism. The CDC categorised these agents into three distinct groups, depending on public health impact (severity of illness and mortality), dissemination potential, public perception, and the easiness of preparation.[2]

Classification for disease prioritisation is a complex decision process.[3] At a state level, disease prioritisation is mainly motivated by the need to allocate limited financial and human resources to achieve the greatest benefit in safeguarding human health. In the broad perspective of public health, the prioritisation of infectious diseases had long been discussed.[4] Although the analytical criteria should be transparent and reproducible, these tasks are daunting because of their interdependence, impairing a separate assessment. The variety of potential bioterrorism pathogens is, by far, greater than the resources that could be allocated to tackle them all at the same time. The case-fatality rate of a provoked infectious event has both social and economic impacts. Therefore, the economic cost might be much higher than the number of human casualties, as was observed in 2001, in the anthrax letter attacks (five deaths *vs* millions of US dollars in the decontamination process expenses).[5]

The European Centre for Disease Prevention and Control reviewed the disease prioritisation methodology in 2015,[6] in a report examining the best practices for ranking infectious disease threats. They compared five methods to prioritise the communicable disease risks with use of bibliometric index, Delphi panels, multi-criteria decision analysis, qualitative algorithms, and questionnaires. Finally, they proposed a tool for disease prioritisation that includes a weighing criterion.[7] For us, this weighing criterion is decisive and should be implemented when a decision is made at a political level. The bioterrorist threat assessment should be regularly re-assessed, because threats can evolve swiftly with viral disease eradications and emergence of new pathogens, including those related to synthetic biology. Moreover, our modern societies are now much more sensitive to unexpected events, with a high media exposure, reflecting the emerging role of social networks. Any low-cost bioterrorist attack, even with a minor clinical impact due to a poorly pathogenic agent, can provoke a global deflagration with an immediate and long-lasting fear cost at the social level. From this standpoint, ever-changing public opinion might be the most important criterion and must be much more taken into account in the bioterrorist risk assessment, preparedness, and response, including an updated ready-to-use communication tool.

Finally, although probably provoking a severe health and societal crisis, bioterrorism is a variation of the natural emergence of infectious diseases. The medical counter-measures against a bioterrorist occurrence or a natural emergence are frequently overlapping, as exemplified by the use of polyclonal serum during an outbreak of anthrax in drug users, or the Ebola vaccine in the outbreaks in Africa this decade.[8,9] Nationally and transnationally, interfacing and strengthening the research, development, and implementation of these counter-measures is clearly beneficial for global health and security. Building efficient communications is a big part of the challenge.

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1 Green MS, LeDuc J, Cohen D, Franz DR. Confronting the threat of bioterrorism: realities, challenges, and defensive strategies. *Lancet Infect Dis* 2018; published online Oct 16. http://dx.doi.org/10.1016/S1473-3099(18)30298-6.

2 Rotz LD, Khan AS, Lillibridge SR, Ostroff SM, Hughes JM. Public health assessment of potential biological terrorism agents. *Emerg Infect Dis* 2002; **8:** 225–30.

3 Brookes VJ, Del Rio Vilas VJ, Ward MP. Disease prioritization: what is the state of the art? *Epidemiol Infect* 2015; **143:** 2911–22.

4 Giesecke J. Choosing diseases for surveillance. *Lancet* 1999; **353:** 344.

5 Schmitt K, Zacchia NA. Total decontamination cost of the anthrax letter attacks. *Biosecur Bioterror* 2012; **10:** 98–107.

6 European Centre for Disease Prevention and Control. Best practices in ranking emerging infectious disease threats—a literature review. 2015. https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/emerging-infectious-disease-threats-best-practices-ranking.pdf (accessed Nov 23, 2018).

7 European Centre for Disease Prevention and Control. ECDC tool for the prioritisation of infectious disease threats-Handbook and manual. 2017. https://ecdc.europa.eu/sites/portal/files/documents/Tool-for-disease-priority-ranking_handbook_0_0.pdf (accessed Nov 23, 2018).

8 Henao-Restrepo AM, Camacho A, Longini IM, et al. Efficacy and effectiveness of an rVSV-vectored vaccine in preventing Ebola virus disease: final results from the Guinea ring vaccination, open-label, cluster-randomised trial (Ebola Ca Suffit!). *Lancet* 2017; **389:** 505–18.

9 Cui X, Nolen LD, Sun J, et al. Analysis of anthrax immune globulin intravenous with antimicrobial treatment in injection drug users, Scotland, 2009–2010. *Emerg Infect Dis* 2017; **23:** 56–65.

The predictive values of the tuberculin skin test and interferon-γ release assays for active tuberculosis development

The prospective cohort study by Ibrahim Abubakar and colleagues reports the predictive values of the tuberculin skin test (TST) and two interferon-γ release assays (IGRAs) for the development of active tuberculosis.[1] The detection of individuals with latent infection who are likely to progress to active disease presents major challenges. 1·7 billion individuals were estimated to be latently infected with tuberculosis globally and about 10% of those will develop active disease.[2] However, there are no available tests that precisely identify which individuals will develop disease. Consequently, preventive treatment is given to at-risk groups that inevitably include individuals who would not have progressed to disease.[3] Additionally, although anti-tuberculosis treatment with 4 months of rifampicin or 9 months of isoniazid can prevent development of active disease from latent infection,[4] poor adherence, toxic effects, and low cost–effectiveness ratio hinder application of these therapies in high-burden low-income countries. Accordingly, a low-cost method of predictive screening for latent tuberculosis is urgently needed. Notably, this study showed that TST-15, a TST with a threshold greater than 5 mm in individuals naive to BCG or 15 mm in those vaccinated with BCG, provided a low-cost screening method to predict the development of disease that was almost as accurate as more expensive IGRAs, even after BCG vaccination.

Abubakar and colleagues did not directly consider the possible effect of non-tuberculosis mycobacteria (NTM) infections, which are also a serious problem in countries with a high burden of tuberculosis. The cross-reactivity might increase the false positivity of TST. By contrast, the immune stimulators used in IGRAs are absent from BCG and NTM strains, and Abubakar and colleagues' study showed that the predictive value of IGRAs was slightly higher than that of TST-15. However, the higher cost of IGRAs hinders their application in lower-income countries. Previously, we reported on the use of recombinant fusion protein ESAT-6–CFP10 for skin tests of tuberculosis infection and showed that it had an accuracy similar to that of IGRAs in diagnosing patients with tuberculosis in clinical trials.[5,6] In a phase 2a trial (NCT02329730),[5] we have further shown that ESAT-6-CFP10 use has similar accuracy to that of T-SPOT.TB in diagnosing tuberculosis infection in healthy volunteers and in patients with active tuberculosis infection (table). Nevertheless, TST-5 (a TST with a threshold of 5 mm) showed significantly higher positivity in healthy volunteers, which indicates high cross-reactivity from BCG vaccination (table). The low cost of this approach will facilitate its application in low-income countries.

Abubakar and colleagues included migrants, defined as people who had arrived within 5 years from high-burden countries, in the high-risk group in their study. This grouping criterion is questionable because many migrants might not have contacted patients with active tuberculosis. In the online appendix, the authors showed that the TST positivity was lower in migrants than in contacts (20·8% *vs* 33·7% in TST-15). Additionally, the percentage of disease progression in migrants was lower than in contacts. Therefore, the inclusion of migrants might have resulted in

	Healthy volunteers			Patients with active tuberculosis		
	Cases	Positive cases	Positivity (%)	Cases	Positive cases	Positivity (%)
TST-5*	56	32	57·1%	53	45	84·9%
ESAT-6–CFP10†	56	4	7·1%	53	43	81·1%
T-SPOT.TB	56	5	8·9%	53	45	84·9%

TST=tuberculosis skin test. *Purified protein derivative skin test with a threshold of 5 mm with a 5 IU inoculation. †ESAT-6–CFP10 skin test with a threshold of 5 mm with a 10 μg antigen inoculation.

***Table*: Use of recombinant fusion protein ESAT-6–CFP10 for skin tests of tuberculosis infection in a phase 2a clinical trial**