

The graph also highlights two HRRs in Texas that have been frequently discussed since the publication of Atul Gawande's *New Yorker* article "The Cost Conundrum": McAllen and El Paso.<sup>3</sup> Unadjusted risk scores suggest that patients in McAllen are 25% sicker than patients in El Paso, but our adjusted estimates suggest that patients in McAllen are only 15% sicker. In other words, in keeping with Gawande's conjecture, a nontrivial share of the difference in measured health between the two areas can be explained by more intensive diagnostic practices by doctors in McAllen than doctors in El Paso. If risk scores were adjusted to account for this finding, the gap in risk score–based reimbursements between McAllen and El Paso would shrink by about 10 percentage points.

The map shows the geographic patterns that emerge from our

risk-score adjustment. Teal areas (in general, the West and Midwest) have patient populations that are less healthy than one would expect on the basis of raw risk scores — that is, they have providers who tend to diagnose less aggressively. Purple areas (in general, the Northeast and South) have patient populations that are more healthy than standard risk-adjustment measures would predict — that is, they have providers who tend to have greater diagnostic intensity. Medicare Advantage payments based on our adjusted risk score measures would tend to increase by as much as 10 to 15% in the dark teal areas of the map and fall by 10 to 15% in the dark purple areas.

Our goal here is to provide an example of how the area-specific adjustment factors we calculated may be useful in practice. We expect that the adjustment factors may also be useful in observa-

tional studies that compare the outcomes of patients in supposedly similar health who are exposed to different treatments, as well as in public reporting programs in which patient choices or physician referrals may be based on risk-adjusted quality measures.

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## New Vaccines against Epidemic Infectious Diseases

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The vaccine-development response to the 2014 Ebola epidemic in West Africa, though a valiant effort, was too little, too late. Three vaccine candidates were tested successfully under challenging conditions.<sup>1-3</sup> Governments and foundations mobilized funds quickly. Companies and research-and-development institutions brought vaccine candidates into the field. Collaborations among the World Health Organization (WHO), funders, academia, civil society, and industry saw

vaccines advancing through more than 15 accelerated clinical trials in a year. But the testing of Ebola vaccine candidates had previously stalled, though several candidates could have been ready for efficacy testing before the epidemic if the necessary investments had been made. In the absence of data on safety, immunogenicity, and dosing in humans, it was challenging to progress quickly with efficacy trials in West Africa. As a result, people who could have been protected instead became

infected, and too many of them died. Moreover, there is no guarantee of similar risk-taking efforts in the future, especially given the poor market potential and the great clinical and regulatory uncertainties.

Vaccines can prevent outbreaks of emerging infectious disease from becoming humanitarian crises. The WHO recently deemed 11 pathogens as the most likely to cause severe outbreaks in the near future and will regularly update its list (see table). There are

feasible vaccine candidates for some of these diseases. When such candidates exist, timely vaccine development can avert global public health emergencies, contain loss of life, and limit social and economic damage.

An efficient global system of vaccine research-and-development preparedness is needed. Since we generally have poor clinical vaccine-development pipelines for epidemic infectious diseases,<sup>4</sup> such diseases can emerge and spread faster than we can successfully develop vaccines. Platform technologies that could reduce development times in an emergency are often not validated for human use in advance, which delays the start of clinical trials. Delays can also result from the time taken to reach agreement on appropriate clinical trial design, even when products are ready for testing. And regulatory pathways are not easily adaptable to epidemic contexts, especially in regions with weaker regulatory capacity and where outbreaks are more likely.

Current vaccine-development efforts are fragmented, with no sustainable mechanism to support them across national borders and direct them toward global epidemic risks. Several countries have invested in research targeting prevention of the emergence and spread of pathogens likely to cause outbreaks that could affect them. But countries at the epicenter of outbreaks of emerging infectious diseases usually lack such research capacity. Uncoordinated government funding cannot efficiently and sustainably address global epidemic risks. Vaccine developers end up spending their own resources to test products for epidemic conditions without any guarantee of

#### Top Emerging Pathogens Likely to Cause Severe Outbreaks in the Near Future.\*

##### Diseases to be urgently addressed under the WHO Research and Development Blueprint

Crimean Congo hemorrhagic fever virus  
 Filovirus diseases (Ebola and Marburg)  
 Highly pathogenic emerging coronaviruses relevant to humans (Middle East respiratory syndrome coronavirus [MERS-CoV], severe acute respiratory syndrome coronavirus [SARS-CoV])  
 Lassa fever virus  
 Nipah virus  
 Rift Valley fever virus  
 Any new severe infectious disease

##### Serious diseases necessitating further action as soon as possible

Chikungunya  
 Severe fever with thrombocytopenia syndrome  
 Congenital abnormalities and other neurologic complications associated with Zika virus

\* Information is from the Research and Development Blueprint for action to prevent epidemics, plan of action, May 2016, World Health Organization. Prioritization criteria included human transmissibility (including population immunity and behavioral factors); severity or case fatality rate; spillover potential; evolutionary potential; available countermeasures; difficulty of detection or control; public health context of the affected areas; potential scope of outbreak (risk of international spread); and potential societal impact. The group of experts who developed the list represented a range of disciplines, including virology, microbiology, immunology, public health, clinical medicine, mathematical and computational modeling, product development, and respiratory and severe emerging infections. The conclusions of the experts were reviewed by the Blueprint's independent Scientific Advisory Group.

risk sharing by governments seeking their help.

To address these problems, leaders from governments, foundations, industry, and civil society came together at the January 2016 World Economic Forum meeting in Davos, Switzerland, and agreed to explore new ways to drive vaccine innovation for high-priority public health threats. The meeting was inspired by a call for a new vaccine fund<sup>5</sup> — and by proposals and expressions of interest from major vaccine manufacturers for new and dedicated partnership structures. It was supported by an emerging consensus from the 2015 Oslo consultation on Financing of R&D Preparedness and Response to Epidemic Emergencies and the process outlined in the WHO Research and Development Blueprint for creating a global financing facility for developing bio-

medical countermeasures against emerging infections. Since the Davos meeting, more than 80 organizations and more than 200 individuals have collaborated to create the Coalition for Epidemic Preparedness Innovations (CEPI). Its mission is to stimulate, finance, and coordinate the development of vaccines against epidemic infectious diseases, especially in cases in which market incentives alone are insufficient.<sup>5</sup>

Between February and June 2016, CEPI convened three expert task teams to assess challenges and potential solutions for pathogen prioritization, clinical development, manufacturing capacity, and regulatory pathways; partnership models; and funding strategies. The teams recommended that CEPI initially draw on the disease priority list in the WHO Blueprint as it gradually develops its own vaccine-prioritization pro-

cess. CEPI will initially focus on investments in essential gaps in product development, especially from late preclinical studies to proof of concept in humans (phase 2 trials); support for technical and institutional platforms that can be used for rapid vaccine development against known and unknown pathogens in the event of a new epidemic; partnership arrangements building on capabilities of advanced vaccine developers and manufacturers; and end-to-end coordination among stakeholders through plans to mobilize resources, manage and distribute stockpiles, and accelerate vaccine testing and approval

accelerate development of feasible vaccines that can have a public health impact and to provide equitable access to affordable vaccines for priority populations. To this end, CEPI has developed a business plan with a budget of \$1 billion for the next 5 years<sup>5</sup> focusing on two main objectives: advancing at least four candidate vaccines against two or three high-priority pathogens to the proof-of-concept stage (by supporting phase 1 and 2 trials) to enable clinical efficacy testing (phase 3) during the initial stages of an outbreak, and building technical and institutional platforms to accelerate the research-and-develop-

tional stockpiles and vaccines available in sufficient quantities in affected territories and for setting prices as low as possible. Product costs should also be minimized through these risk-sharing arrangements.

A Joint Coordination Group was established in November 2016 to help align CEPI's efforts with those of other organizations in order to facilitate early development and to address clinical, regulatory, access, and manufacturing issues. CEPI will soon issue its first requests for proposals for funding, focusing on pathogens prioritized by its scientific advisory committee. CEPI also aims to collaborate with procurement agencies to facilitate investments in vaccine stockpiles for emergency use beyond its own investments in smaller investigational stockpiles.

CEPI is in a strong position, with several governments and foundations having promised investments to meet its budgeted needs for 5 years. We have already partnered with experienced vaccine manufacturers with global reach, members of the Developing Countries Vaccine Manufacturers Network, and vaccine biotechnology companies. We have accumulated expertise through our task teams and working groups and have benefited from the evidence generated through the WHO Research and Development Blueprint process. To succeed, we will have to continue to attract and retain a broad range of top experts and institutional champions.

Without cross-sector coordination or focus on timely vaccine-development capabilities, even the effort mounted against Ebola will be hard to replicate. We hope that CEPI's capabilities and partner-

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during epidemics. Priority will also be given to contributions to finishing the job on Ebola vaccines.

Building on the task teams' recommendations, CEPI has transitioned into a startup phase. An international nonprofit association has been founded by the governments of Norway and India, the Wellcome Trust, the Bill and Melinda Gates Foundation, and the World Economic Forum, and CEPI stakeholders are invited to become formal partners. An interim board and scientific advisory committee have been appointed. An interim secretariat is ensuring CEPI's launch, with functional nodes in Norway, the United Kingdom, and India.

CEPI will measure key outcomes to assess its capacity to

ment response to the emergence of pathogens. CEPI will plan for and mobilize resources for phase 3 efficacy trials as well as support small stockpiles, and it is exploring ways of supporting research and development of multivalent Ebola vaccines and facilitating regulatory preparedness and stockpiling.

CEPI plans to ensure the sustainability of its partnership approach by securing industry participation in collaborations in which the risks and benefits of vaccine development are shared and by supporting the development of regional capabilities for epidemic vaccine preparedness. To ensure achievement of public benefit, CEPI and its partners will need to agree to reasonable obligations for making investiga-

ships will enable it to adequately address epidemic vaccine-development needs and help contain outbreaks quickly, providing a sort of global health insurance policy. We look forward to collaborating with all relevant actors to achieve these goals.

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## The Common Rule, Updated

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For the first time since it was issued in 1991, the Common Rule — the set of federal regulations for ethical conduct of human-subjects research — has been updated. Most of the new requirements, many of which increase flexibility, will go into effect in 2018, which gives institutions a year to work toward implementation.

The public saw the beginnings of this effort in 2011, when the Department of Health and Human Services issued an Advance Notice of Proposed Rulemaking, signaling an interest in modernizing the regulations by enhancing protections for human research participants and reducing unnecessary burden and ambiguity for researchers.<sup>1</sup> In September 2015, a Notice of Proposed Rulemaking (NPRM) identifying numerous proposed changes was released for public comment, generating a robust and energetic discussion of the proposals' merits.<sup>2</sup> More than 2100 comments were

submitted, from a fairly wide swath of the public, including individuals, institutions, organizations, and societies. These comments, and influential reports including one from the National Academies of Sciences, Engineering, and Medicine,<sup>3</sup> led to a long process of deliberation and discussion. The result is a final rule that differs significantly from what was initially proposed.

Most notably, the new rule does not adopt the proposal to cover researchers' use of unidentified biospecimens (such as leftover portions of blood samples) and to require informed consent for such research. This proposal generated far more comments than any other, and by a substantial margin those comments opposed the proposal. Commenters in every category — institutions, researchers, people working in programs that protect research participants, and people with no employment connection to the research world — expressed con-

cern that implementing this proposal could significantly harm the ability to do important research, without producing any substantial off-setting benefits. The public response was particularly noteworthy, given that the premise behind the proposal was specifically tied to public sentiment: the NPRM had stated that continuing to allow research on unidentified biospecimens without consent would place “the publicly-funded research establishment in an increasingly untenable position because it is not consistent with the majority of the public's wishes.” That premise now seems questionable. Accordingly, the proposals that would have made it harder to do research with unidentified biospecimens are not included in the new rule.

The rule also does not include proposals that were unpopular at least in part because they were dependent on additional rules or criteria that were not yet developed (and thus could not be