COMMENTS AND RESPONSES

Effect of Ebola Progression in Liberia

TO THE EDITOR: Yamin and colleagues (1) evaluated the probability of eliminating Ebola by case isolation of 50% to 100% of nonsurvivors compared with isolation of all infected persons when the type of contact is dominated by conversation or by sharing a meal or a bed. However, they do not mention the transmission of the virus during conversation, or aerosol transmission. Masks are protective only when they are of good quality and properly used.

Filoviruses are classified as category A bioterrorism agents by the Centers for Disease Control and Prevention and are thought to be aerosol-mediated. Countering aerosolized filovirus infection has been a major priority of biodefense research (2). Transmission of Marburg virus by exposure to bat-inhabited caves and mines has already been reported (3). In a study by Reed and associates, when cynomolgus and rhesus macaques and African green monkeys were exposed to aerosolized Zaire ebolavirus, all 3 species developed similar clinical signs and symptoms and the outcome resembled that of parenteral inoculation with the virus for each species (4).

Rhesus monkeys who experimentally inhaled droplets of 0.8 to 1.2 microns containing Ebola virus died of ebolavirus disease within a few days. Immunocytochemistry has also shown Ebola virus antigens in airway epithelium, alveolar pneumocytes, and macrophages in the lung and mediastinal lymph nodes. Aggregates of characteristic filamentous virus were present in type 1 pneumocytes, macrophages, and air spaces of the lung by electron microscopy (5). Similar lethal infections by aerosol exposure were reported in 18 rhesus macaques, including early infection of the respiratory lymphoid tissues (6), and aerosol exposure to Zaire ebolavirus has been reported to cause lethal infections in rhesus monkeys. Two rhesus monkeys were exposed to 400 plaque-forming units of the virus and 2 others to 50 000 plaque-forming units; all 4 monkeys developed diseases and died 7 to 9 days after exposure (5).

In a fatal disease like Ebola, where human experimentation cannot be used to prove the route of transmission, evidence available from nonhuman primates should be taken seriously. However, the absence of evidence in humans is not evidence of the absence of aerosol transmission. Demonstration of fatal aerosol transmission of Ebola virus in monkeys reinforces the importance of taking appropriate precautions to prevent its potential aerosol transmission to humans. We request that Yamin and colleagues discuss these issues related to their study to clear the air.

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TO THE EDITOR: Case isolation has been the method of choice for dealing with disease epidemics for hundreds of years. Yamin and colleagues (1) improve on our knowledge of how to truncate the human–human transmission of a communicable disease by estimating the time during which case isolation is most effective for patients with Ebola, namely, within 4 days of symptom onset. Because rapidly fatal diseases for which no effective treatment is available tend to be self-limiting, can the authors estimate how long the Ebola pandemic will continue before it dies out on its own?

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IN RESPONSE: The Ebola outbreak that swept across West Africa has been unprecedentedly devastating, yet recently showed encouraging signs for containment in Liberia (1). In our study, we integrated data on daily viral load and contact patterns of patients with Ebola to evaluate the effectiveness of nonpharmaceutical interventions to curtail transmission in Liberia. We modeled transmission by considering 3 potential transmission routes: sharing a bed, a meal, and a conversation.

Our findings suggest that viral load had a greater effect on the probability of transmission from less intimate forms of contact where aerosol transmission is conceivable, such as sharing a conversation, than from more intimate forms of contact, such as sharing a bed. Consequently, even if aerosol transmission were possible, as Drs. Mohapatra and Mishra suggest, our main results would be even more robust. Specifically, nonsurvivors have a higher viral load, particularly after 4

days from symptoms onset. Thus, nonsurvivors cause more transmission than survivors, making early isolation of the most severely ill patients paramount to reducing household and community transmission.

Despite the exponential epidemiologic trajectory in Liberia during our study, we showed that targeting persons in critical condition within 4 days had a high probability of eliminating Ebola in Liberia. Furthermore, this intervention effort is logistically feasible, particularly because contact tracing has improved and Ebola treatment units have scaled up in recent months (2). We have now extended our analysis to predict when Ebola could have been eliminated in Montserrado County and the expected number of cases if various isolation strategies had been initiated on 17 September 2014, the last data point of our previous study.

If all nonsurvivors could be isolated on the fourth day of symptoms, the median time to elimination in Montserrado County would be 162 days (interquartile range [IQR], 119 to 281 days) and the median number of total cases would be 1657 (IQR, 1471 to 2142). If all nonsurvivors could be isolated on the third day after symptom onset, the median time for elimination would decrease to only 90 days (IQR, 65 to 138 days) with a median number of total cases of 1352 (IQR, 1278 to 1522) from the point of implementation. Conversely, if only 75% of nonsurvivors could be targeted on the fourth day of symptoms, the probability for elimination would be 74% with a median elimination time of 378 days and an epidemic magnitude of 2791 cases. These findings highlight the importance of exhaustive efforts to trace contacts and of educational campaigns to maintain awareness about Ebola symptoms and encourage symptomatic persons to seek health care until the Ebola outbreak is finally eliminated.

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Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD)

TO THE EDITOR: Collins and colleagues' article (1) is important because prediction is becoming an integral part of clinical medicine. I was gratified to note their statement that all predictions must be time-denominated (2). The authors suggest that there are only 2 types of predictions, diagnostic and prognostic, and subsume risk predictions within diagnostic predictions. I have suggested that risk is a third type of prediction (3).

Risk and diagnostic predictions differ in their targets, degrees of predictive accuracy, and time intervals. In diagnostic predictions, we wish to predict whether a person has detectable disease, the disease's time interval is instantaneous, and the prediction must be nearly 100% accurate. In risk predictions, we wish to predict the probability that a person will have detectable disease over a specified time interval and the prediction must be less than 100% accurate. These predictions differ greatly, and the distinction between risk and diagnosis is important for reporting prediction studies.

We pose 3 additional points. First, the authors do not mention the problem of "lifetime" predictions. Second, they state, "In case of poor performance, the model can be updated or adjusted on the basis of the validation data set." However, they do not say that the updating or adjustment means that the investigators have looked at their results, which indicates that they must do another, independent external validation study. Finally, because most of the medical prediction literature currently consists of bivariate studies (4), I am uncertain why the authors' prescriptive reporting requirements include only multivariate studies.

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IN RESPONSE: The Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) Statement concerns prediction models that are developed for diagnosis or prognosis. We believe that the additional type of prediction that Dr. Burke refers to as "risk prediction" is subsumed within the prognostic framework. Prognostic models as referred to in TRIPOD predict a certain health condition (such as death, a disease, a complication, a recurrent event, or any other outcome) over a specified period in participants at risk for this condition. Therefore, prognostic models may address ill or healthy persons, such as by predicting the 1-year probability of dying for a patient with lung cancer or the long-term (for example, 10-year) probability of cardiovascular disease for a healthy person.

As Dr. Burke correctly points out, we did not explicitly mention the issues of models for predicting lifetime risk. How-

ever, studies of this type of prediction model fit entirely within the remit of TRIPOD. We decided not to explicitly discuss these issues because a model for predicting lifetime risk is unlikely to be developed. If interest in these models increases, these issues will undoubtedly be explicitly mentioned when TRIPOD is revised and updated. However, as previously discussed, we believe that these models are just examples of models predicting long-term outcomes in (healthy) general populations.

We completely agree that any updated model should be further evaluated in a separate data set. In our accompanying article, we stress that "The updated model is in essence a new model. . . . Updated models, certainly when based on relatively small validation sets, still need to be validated before application in routine practice" (1).

Dr. Burke's final comment concerns single-marker (biomarkers and prognostic factors) studies. Although multivariable prediction model studies and single-marker studies that apply some form of multivariable analysis are clearly similar, the differences are noticeable. That such multivariable analysis is being applied does not necessarily make it a prediction model study. The delineating factor is that one develops, validates, or updates a multivariable prediction model that, as such, can be used to produce a probability (or risk) estimate for a person. In other words, TRIPOD addresses models that allow for *individualized predictions*. "Individualized" can be considered the most important word in the TRIPOD acronym. For studies of single markers, authors should ensure complete and accurate reporting following the reporting recommendations for tumor marker prognostic studies guideline (2).

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Screening for Vitamin D Deficiency

TO THE EDITOR: We read LeBlanc and colleagues' review (1) with great interest. Approximately twice as many meta-analyses have been done on vitamin D supplements for falls and fractures as randomized trials. Conclusions of these meta-analyses differ largely because of the methods adopted, such as the choice of studies included (2, 3). LeBlanc and colleagues assessed the effectiveness of vitamin D supplementation on mortality, falls, and fractures in vitamin D deficiency, including 11, 5, and 5 trials, respectively, for each outcome. In contrast, we included 38, 20, and 23 trials, respectively, in meta-analyses of vitamin D supplementation for these conditions (4, 5). The differences in study inclusion are largely due to LeBlanc and colleagues' requirement that baseline 25-hydroxyvitamin D [25-(OH)D] levels be measured in all participants. They aimed to include only studies in which 90% of participants had 25-(OH)D levels less than 75 nmol/L, but random sampling of baseline levels is sufficient to assess this criterion. Baseline 25-(OH)D levels were reported in a sample or in all participants in most (34 of 42) trials in our meta-analyses, with 25 of 32 (78%) reporting mean baseline 25-(OH)D levels less than 50 nmol/L; thus, 90% of participants most likely had 25-(OH)D levels less than 75 nmol/L.

Inconsistency in study and participant inclusion is an additional consequence of LeBlanc and colleagues' methods. Of 2 studies done by the same investigators in the same population group, 1 was included in which 25-(OH)D levels were measured in all participants; the other was excluded because these levels were measured in only a subset of participants even though mean baseline 25-(OH)D levels were similar in the 2 studies. Likewise, a small subset of participants in 2 studies was included in this meta-analysis because they were selected to have baseline 25-(OH)D levels measured, whereas most participants in both studies were excluded.

The upshot is that LeBlanc and colleagues' meta-analyses contain few events and participants and do not include most studies with fracture or falls as the primary end point. Previous reviews on vitamin D for the U.S. Preventive Services Task Force also have not included eligible studies. Consequently, conclusions based on these reviews may not be reliable.

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TO THE EDITOR: The U.S. Preventive Services Task Force has concluded that the current evidence is insufficient to assess the balance of benefits and harms of screening for vitamin D deficiency in asymptomatic adults. As LeBlanc and colleagues' review (1) shows, this evidence comprises studies whereby supplementation (variable doses of vitamin D_2 or D_3 with or without calcium) has been monitored mainly by measuring total concentrations of 25-(OH)D. Instead, future studies should focus on assessing concentrations of bioavailable vitamin D.

Concentrations of total 25-(OH)D and 1,25-dihydroxyvitamin D measured routinely in daily practice are known to differ from those of bioavailable vitamin D. Free and bioavailable vitamin D concentrations depend on the vitamin D–binding protein and ethnicity (2). In addition, we need evidence of techniques to increase concentrations of bioavailable vitamin D, such as obtaining more outdoor physical activity, which might increase biosynthesis and bioavailable concentrations of vitamin D_3 and circumvent hypervitaminosis D (3). Harmful effects of hypervitaminosis D might be due solely to excess biosynthesized sequestrated vitamin D as a result of inappropriate oral supplementations and of not being converted to active bioavailable vitamin D. Excess vitamin D is arteriotoxic and causes elastocalcinosis, which induces destruction of elastic fibers, leads to arterial stiffness, and causes arterial calcification through upregulation of 1,25-dihydroxyvitamin D_3 receptors and increased calcium uptake in smooth-muscle cells of the arteries (4, 5).

Research resources are finite in these times of austerity; hence, they should be allocated appropriately. Robust and pertinent evidence is needed to formulate educational and interventional policies that can be implemented to prevent the global public health problem of cardiometabolic diseases and autoimmune and neoplastic conditions associated with decreased bioavailable concentrations of vitamin D.

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TO THE EDITOR: LeBlanc and colleagues (1) conclude that treatment of vitamin D deficiency in asymptomatic adults might reduce the risk for falls but not fractures. This conclusion requires an explanation, because a fall is one of the strongest risk factors for a fracture. We present an evidence-based, mechanistic insight into this unexpected result.

Muscle force is related to bone strength, and the risk reduction of falls but not fractures (1) theoretically means that treatment of vitamin D deficiency reduces fall risk by improving balance (rather than muscle force) but does not change fracture risk by impairing bone strength. The former would be consistent with clinical evidence, whereas the latter could be associated with skeletal adaptation to the mechanical environment (2–5). Bone begins to deform plastically at a yield force, and normal physical activity causes the preyield "elastic" deformation (strain) of bone. A decrease in bone quality associated with minerals induces an increase in the "elastic" deformation, whereas the skeleton responds to the mechanical environment to maintain the resultant strain of bone. Consequently, mineral-related impairment of bone quality can be compensated by mechanical strain–related feedback control and might decrease bone fragility if compensated efficiently (3). For example, patients with hypophosphatemic rickets or osteomalacia have a lower quality and higher quantity of bone (2). Vitamin D deficiency impairs bone quality, and children with nutritional rickets would also have bigger, long bones (4). Furthermore, a recent study in children with cerebral palsy showed an inverse correlation between serum levels of 25-(OH)D and *Z* scores for areal bone mineral density in the distal femur (4). Of note, the latest meta-analysis in adults found that supplementation with at least 800 IU/d of vitamin D has fewer effects on areal bone mineral density than supplementation with less than 800 IU/d of vitamin D in the lumbar spine and potentially the femoral neck but not the forearm (5).

Finally, many observational studies have shown an association between lower levels of 25-(OH)D and higher incidences of fracture in adults. However, LeBlanc and colleagues' conclusion suggests that confounding biases the association. Vitamin D status is strongly influenced by sunlight exposure associated with outdoor activity, whereas mechanical loading from habitual physical activity is the primary determinant of bone strength. These factors imply that higher incidences of fracture could result from lower levels of physical activity rather than of 25-(OH)D.

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IN RESPONSE: The purpose of our systematic review was to determine whether screening for vitamin D deficiency in asymptomatic persons improved health outcomes. Therefore, we determined a priori that we would include only studies of populations that had documented vitamin D deficiency and were not selected on the basis of a history of osteoporosis, prior fractures, or falls. Thus, we included fewer studies than the meta-analyses by Dr. Bolland and colleagues (1, 2), which also included trials of participants with normal vitamin D levels and with osteoporosis and prior fractures or falls. We did not exclude any study solely because only a random sample of the population had vitamin D deficiency according to our definition [90% of persons with 25-(OH)D levels <75 nmol/L]. Either the subsample did not meet this deficiency definition or the study was excluded because of another reason (for example, patients had prior fractures or falls). In the specific example mentioned by Dr. Bolland and colleagues (3, 4), the study of the subsample of participants was excluded because the subsample population did not meet our criterion for deficiency; however, the overall trial was included because when 25-(OH)D levels were measured in all participants, more than 90% were deficient. Although some of our analyses had relatively few events, expanding inclusion to clinically heterogeneous populations that are not of interest in order to increase statistical power would not have been appropriate.

We agree with Dr. Kain that research on the role of bioavailable vitamin D levels is important to better understand the effects of vitamin D treatment on clinical outcomes. We also agree with Dr. Sugiyama and associates that research is needed on mechanisms for how vitamin D might prevent falls but not fracture.

In response to Heaney and Armas' editorial (5), we explicitly defined the scope of the review before starting the work. We addressed the factors raised in the editorial as potentially affecting estimates in sensitivity and stratified analyses. Further stratifying or restricting the analysis, as Heaney and Armas suggested, would result only in even less evidence to support the benefits of vitamin D treatment.

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Screening for Vitamin D Deficiency: Is the Goal Disease Prevention or Full Nutrient Repletion?

TO THE EDITOR: We read Heaney and Armas' editorial (1) about the assessment of and need for vitamin D supplementation with great interest. The pathologic hallmark of vitamin D insufficiency is an increase in uncalcified osteoid organic matrix in bone. The clinical hallmarks of this condition are specific findings, such as Milkman fractures, or unmineralized osteoid on undecalcified bone biopsy specimens. Neither hypocalcemia nor osteoporosis—which causes uniform loss of organic and mineralized bone and is a disorder of architecture, not calcification—is a hallmark of vitamin D deficiency. Virtually no direct clinical evidence of vitamin D deficiency in the general U.S. population is available.

Vitamin D deficiency has most often been diagnosed by blood levels of an inactive intermediate, the 25-hydroxyvitamin D [25-(OH)D] metabolite. Little strong evidence indicates any relationship between this inactive metabolite and the active metabolite, 1,25-dihydroxycalciferol, in the blood. Strong clinical data of any relationship between 25-(OH)D and proven vitamin D deficiency states is lacking. It is critical to remember that meta-analyses, epidemiologic studies, and correlational studies do not—and cannot—provide causal data.

No studies have been done that have met the gold standard of being well-controlled and randomized with appropriate statistical analyses on which to base the current judgments about the need for vitamin D supplementation in the U.S. general population. Given this lack of solid evidence, as supported by the U.S. Preventive Services Task Force's recommendation statement (2), supplementation with more than a minimal dose of vitamin D or screening in populations other than those at risk for vitamin D deficiency (such as persons with malabsorption syndromes) should not be undertaken. For those at risk, measurement of 25-(OH)D may not be the best way to assess vitamin D status.

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IN RESPONSE: Dr. Chausmer identifies rickets and osteomalacia as the only manifestations of vitamin D deficiency and presumably considers their prevention to be the principal effect of vitamin D, which is incorrect. Rickets and osteomalacia are probably the most evident and severe manifestations, but more than 90% of vitamin D acts outside of the calcium and bone economies and is involved in gene transcription essential for the function of most tissues (1). 1,25-Dihydroxyvitamin D [1-25$(OH)_2$D], needed for that function, is not carried to the cells through the blood but is synthesized intracellularly by the tissues concerned precisely when they need it to mount a response to myriad physiologic and exobiotic signals. The 1,25-$(OH)_2$D used by various tissues cannot be measured in the serum because it never existed there. However, 25-(OH)D can be measured. This metabolite is the substrate for tissue-level 1-α-hydroxylases, and its concentration limits intracellular 1,25-$(OH)_2$D production.

Measuring 1-α-hydroxylase is important not because 25-(OH)D is fortuitously a marker for vitamin D status but because it tells us precisely what the tissues "see" when they need to make 1,25-$(OH)_2$D and because its availability limits the speed and extent of tissue response. For example, Liu and colleagues (2) showed definitively that the ability of macrophages to combat the tubercle bacillus was a direct function of serum 25-(OH)D concentration. In another, lesser-known manifestation, human breast milk contains virtually no vitamin D at prevailing maternal vitamin D status values but fully meets an infant's need for vitamin D when maternal 25-(OH)D levels are greater than 112 nmol/L (3), a value that, not surprisingly, coincides exactly with values in East Africans following ancestral lifestyles (4).

It is important to understand that the function of vitamin D and the other micronutrients is facilitative. They are necessary for cell function but not causative thereof. In the absence of physiologic need, they do nothing, and increasing their intake has no proper effect. The definition of adequacy for all the micronutrients should not be the absence of some disease (rickets, beriberi, and scurvy) but the optimal functioning of all body systems. The need varies by system; it is relatively high for lactation (>112 nmol/L) and somewhat less so for optimal skeletal mineralization (>75 nmol/L). However, the requirement for the whole organism is the intake that supports all physiologic functioning. Because response to dosing varies widely (with a coefficient of variation of nearly 40%), we can be assured that we have achieved the proper level only by measuring serum 25-(OH)D concentrations.

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Disclosures: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M14-2573.

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CORRECTIONS

Correction: Pharmacologic Interventions for Painful Diabetic Neuropathy

A recent article (1) was missing the estimates for pregabalin versus placebo in the Data Synthesis section of the abstract and in the section Meta-analysis by Individual Drugs. The values are as follows: pregabalin (standardized mean difference, −0.55 [credible interval, −0.94 to −0.15]).

This has been corrected in the online version.

Reference

1. Griebeler ML, Morey-Vargas OL, Brito JP, Tsapas A, Wang Z, Carranza Leon BG, et al. Pharmacologic interventions for painful diabetic neuropathy. An umbrella systematic review and comparative effectiveness network meta-analysis. Ann Intern Med. 2014;161:639-49. [PMID: 25364885] doi:10.7326/M14-0511

Correction: Efficacy of Commercial Weight-Loss Programs

In a recent article (1), Table 6 of the Supplement, which reports adverse events, has been revised to correct several errors. With the addition of this corrected table, the authors

would also like to highlight relevant changes that would apply to the original article text. The article previously stated that no studies of Nutrisystem reported adverse events, which should state instead that harms occurred rarely when reported. The article previously stated that 6.3% of Health Management Resources participants experienced cholecystectomy, which was an error and has been removed. The article previously stated that the Medifast study did not report adverse events, which should state instead that no serious harms occurred. The article previously stated that harms occurred rarely among Atkins participants, which should instead state that Atkins participants reported constipation.

This has been corrected in the online version.

Reference

1. Gudzune KA, Doshi RS, Mehta AK, Chaudhry ZW, Jacobs DK, Vakil RM, et al. Efficacy of commercial weight-loss programs. An updated systematic review. Ann Intern Med. 2015;162:501-12. [PMID: 25844997] doi:10.7326/M14-2238