THE AUTHORS REPLY: Swartz comments that patients in our study did not have a significant reduction in the rate of all-cause community-acquired pneumonia or death. Of note, our study was neither designed nor powered for those exploratory end points. Efficacy was shown for the prevention of confirmed community-acquired pneumonia by any pneumococcal strain, with a vaccine efficacy of 30.6% (95% CI, 9.8 to 46.7). Weinberger at al. suggest that the vaccination of adults 65 years of age or older will have minimal effects. The 5% reduction in the rate of all-cause community-acquired pneumonia, although not a significant change, is in line with the 12% prevalence of vaccine serotypes in all episodes of all-cause community-acquired pneumonia in the placebo group. The absolute numbers of infections that are prevented will depend on the burden of disease caused by PCV13 serotypes in elderly persons, and these data will influence the cost-effectiveness of routine use of PCV13 in this population. Naturally, such use may differ in various countries.

Given that vaccine-type pneumococci are estimated to be responsible for approximately 10% of all-cause community-acquired pneumonia in the United States,[1,2] analysts at the Centers for Disease Control and Prevention have predicted that adding a dose of PCV13 to the current schedule for the 23-valent pneumococcal polysaccharide vaccine (PPSV23) for adults who are 65 years of age or older could prevent an estimated 230 cases of invasive pneumococcal disease and 12,000 cases of community-acquired pneumonia over the lifetime of a cohort of persons in this age group in the United States, assuming current indirect effects from child immunization and current PPSV23 vaccination coverage.[3,4]

In our study, of the 3232 sentinel-center visits by patients with suspected pneumonia or invasive pneumococcal disease, 146 patients were not hospitalized. Of these patients, only 3 had a first episode of vaccine-type pneumococcal community-acquired pneumonia (2 in the PCV13 group and 1 in the placebo group).

Using our study data, Leo estimates the numbers of persons who would need to be treated to prevent one case of pneumonia or one case of invasive pneumococcal disease. However, estimates of the NNT differ from estimates of the number needed to vaccinate (NNV), which can be biased, inaccurate, and therefore misleading when derived from a multiyear, event-driven study such as CAPITA.[5] Despite our efforts to capture all events of community-acquired pneumonia, we would have missed some episodes, and in 7% of the episodes of suspected pneumonia, urine samples for antigen detection could not be obtained, thus reducing the likelihood of the detection of PCV13 serotypes as causative. Moreover, the NNV, a value that has no defined favorable threshold, is limited in its ability to independently predict a health benefit. Furthermore, participants in a large, randomized study may not be representative of the general population. Consequently, our study may not be the best one for a determination of the NNV.

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1. Sherwin RL, Gray S, Alexander R, et al. Distribution of 13-valent pneumococcal conjugate vaccine Streptococcus pneumoniae serotypes in US adults aged ≥50 years with community-acquired pneumonia. J Infect Dis 2013;208:1813-20.
2. Grijalva CG, Wunderink RG, Williams D, et al. Distribution of pneumococcal serotypes detected through urine analysis among US adults hospitalized with pneumonia after introduction of PCV13. Presented at the 9th International Symposium on Pneumococci and Pneumococcal Disease (ISPPD-9), Hyderabad, India, March 9–13, 2014. abstract.
3. Stoecker C. Incremental cost-effectiveness of modifying PPSV and PCV recommendations for adults age 50 and over. Presented at the June 2014 Meeting of the Advisory Committee on Immunization Practices, Atlanta, June 25, 2014 (http://www.cdc.gov/vaccines/acip/meetings/slides-2014-06.html).
4. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged ≥65 years: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep 2014;63:822-5.
5. Tuite AR, Fisman DN. Number-needed-to-vaccinate calculations: fallacies associated with exclusion of transmission. Vaccine 2013;31:973-8.
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Chikungunya Virus Infections

TO THE EDITOR: Weaver and Lecuit's review (March 26 issue)[1] on chikungunya fever mentions that the disease may alter the quality of life for up to 6 years.[2] On the basis of our clinical experience, two types of persistent post–chikungunya fever rheumatic disorders can be distinguished.[2]

Approximately 95% of patients who still have pain beyond 3 months after acute infection have varied musculoskeletal features but not polyarthritis and have substantial improvement with prolonged administration of nonsteroidal antiinflammatory drugs (strictly limiting the use of glucocorticoids), analgesics, and local treatment, including physiotherapy.[3] In contrast, the conditions of the other 5% of patients meet the criteria for chronic inflammatory rheumatism (rheumatoid arthritis, spondyloarthritis, or unclassified polyarthritis), with a potentially destructive course,[2,4] and require disease-modifying antirheumatic drugs (such as methotrexate), as recommended by rheumatologists.[3] These two distinct post–chikungunya fever profiles need to be distinguished in the assessment of therapeutic trials or biomedical studies, because the underlying immune and viral mechanisms (including antigen clearance and replicative sanctuaries) are likely to differ between them.[5] An understanding of post–chikungunya fever pathogenesis is essential to improve therapeutic strategies for millions of affected patients worldwide.

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1. Weaver SC, Lecuit M. Chikungunya virus and the global spread of a mosquito-borne disease. N Engl J Med 2015;372:1231-9.
2. Javelle E, Ribera A, Degasne I, Gaüzère BA, Marimoutou C, Simon F. Specific management of post-chikungunya rheumatic disorders: a retrospective study of 159 cases in Reunion Island from 2006-2012. PLoS Negl Trop Dis 2015;9(3):e0003603.
3. Simon F, Javelle E, Cabié A, et al. French guidelines for the management of chikungunya (acute and persistent presentations) November 2014. Med Mal Infect (in press).
4. Ganu MA, Ganu AS. Post-chikungunya chronic arthritis — our experience with DMARDs over two year follow up. J Assoc Physicians India 2011;59:83-6.
5. Hoarau JJ, Jaffar Bandjee MC, Krejbich Trotot P, et al. Persistent chronic inflammation and infection by Chikungunya arthritogenic alphavirus in spite of a robust host immune response. J Immunol 2010;184:5914-27.

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TO THE EDITOR: During the 2014 chikungunya fever outbreak on Martinique Island, some 144,000 patients (37% of the population) presented with acute symptoms. Severe disease with acute organ dysfunction has been described in 240 patients with proven chikungunya fever and was responsible for 47 deaths, all due to coexisting conditions. Subsequently, the treatment of patients with the chronic stage of chikungunya fever (defined as the persistence of symptoms after week 12) has been a challenge. In a study of a prospective cohort of 224 outpatients with proven acute chikungunya fever, we found persistent symptoms at week 12 in 61% of patients and at week 24 in 49% of patients. The persistent symptoms were mainly musculoskeletal pain, neuropathic pain, or both; chronic inflammatory rheumatism was also observed. Providing care for those with the chronic manifestations has been difficult and has led us to open a service for specific consultation. General physicians can refer their patients with complex coexisting conditions to a team of pain specialists, physiotherapists, rheumatologists, psychiatrists, and infectious-disease specialists working in concert. In our experience, this multidisciplinary care for patients with the chronic stage of chikungunya fever is essential and should be initiated at the beginning of any new epidemic.

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THE AUTHORS REPLY: We thank Simon and colleagues for stressing, as we wrote in our review, that not all patients who have chikungunya virus infection with chronic symptoms have arthritis or fulfill the criteria for having chronic inflammatory rheumatism. In fact, patients with chronic inflammatory rheumatism represent only a minority, as estimated by Simon and colleagues, at approximately 5%. Future studies involving multiple patient cohorts from diverse geographic and ethnic backgrounds and infected with chikungunya virus strains from diverse lineages are needed to refine the estimates of arthritis development, as well as the predictors for this outcome. This information is indeed important, be-

cause there is a need to define the disease burden and costs associated with chikungunya virus infection, and there are important therapeutic implications underscored by Simon et al., because disease-modifying drugs such as methotrexate should be prescribed only to patients who truly have chronic inflammatory rheumatism. Little is known regarding the underlying mechanisms of the symptoms of chronic chikungunya fever, including the viral and host factors responsible for rapid recovery versus the development of chronic musculoskeletal symptoms, arthralgia, arthritis, or destructive arthritis. This constitutes a major scientific challenge that will require both experimental systems and detailed analyses involving appropriate patient cohorts.

Cabié and colleagues share the results of their first clinical analysis involving patients infected with chikungunya virus in Martinique. They confirm that the high incidence of chronic symptoms associated with Indian Ocean lineage virus strains circulating in Asia is also observed with the Asian strains recently introduced from Asia into the Americas. It is also important to stress that, given the variety of chronic symptoms associated with chikungunya virus infection, the absence of biomarkers to monitor disease progression, and the very limited therapeutic options available, providing patients with access to a multidisciplinary outpatient clinic can be very helpful in disease management.

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Fibrosis — A Common Pathway to Organ Injury and Failure

TO THE EDITOR: In their review, Rockey et al. (March 19 issue)[1] do not include drugs as a possible trigger of lung and cardiac fibrosis. A well-recognized cause of pulmonary fibrosis is drugs — in particular, antineoplastic agents such as bleomycin, busulfan, cyclophosphamide, and carmustine.[2] Other drugs, such as nitrofurantoin, amiodarone, procainamide, flecainide, and penicillamine, have also been implicated. The prognosis in patients with fibrosis induced by alkylating agents is often poor, and the mortality rate is high. The changes in the lung include fibrosis of the alveolar septa and enlargement of the type II alveolar-lining cells.[2] Drug-induced pulmonary fibrosis may involve the release of free oxygen radicals and various cytokines such as transforming growth factor β1 and tumor necrosis factor α.[2] Treatment consists of discontinuing the drug; the administration of glucocorticoids may be necessary in some cases. Drug-induced fibrotic valvular heart disease is also not mentioned in the article, although ergot derivatives, the appetite suppressants fenfluramine and dexfenfluramine, and the dopamine agonists pergolide and cabergoline have been implicated.[3] Interference with serotonin metabolism and its associated receptors and transporter gene seems a likely mechanism for the development of drug-induced valvular heart disease.[4]

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1. Rockey DC, Bell PD, Hill JA. Fibrosis — a common pathway to organ injury and failure. N Engl J Med 2015;372:1138-49.
2. Ben-Noun L. Drug-induced respiratory disorders: incidence, prevention and management. Drug Saf 2000;23:143-64.
3. Bhattacharyya S, Schapira AH, Mikhailidis DP, Davar J. Drug-induced fibrotic valvular heart disease. Lancet 2009;374:577-85.
4. Hutcheson JD, Setola V, Roth BL, Merryman WD. Serotonin receptors and heart valve disease — it was meant 2B. Pharmacol Ther 2011;132:146-57.

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TO THE EDITOR: In their article discussing fibrosis as a common pathway to organ failure, Rockey et al. report that retroperitoneal fibrosis, a rare idiopathic fibroinflammatory condition often causing ureteral obstruction, has no available treatment. This is not entirely true. A number of therapeutic strategies have proved effective for this disease. Glucocorticoids are commonly used, since they lead to considerable shrinkage of the retroperitoneal mass and can relieve ureteral obstruction. A randomized, controlled trial showed that prednisone is superior to tamoxifen, a wide-