Pneumonia is one of the most frequent serious complications of stroke. It is independently associated with a 3-fold increase in in-hospital mortality, higher hospital costs, and worse functional outcomes. Given the clinical impact, efforts to reduce this complication are important. Pneumonia prediction models have been developed for clinical use and various interventions to prevent pneumonia have been evaluated, but more research in these areas is needed. The ability to synthesize the literature is difficult because of the variability in the frequencies of pneumonia reported across studies, which is further complicated by differences in definitions of pneumonia used in clinical studies.

The study by Kishore et al is an important initial step in organizing the approach to study this important stroke issue. The authors are a part of the multidisciplinary group Pneumonia In Stroke ConsEnsuS (PISCES), whose goal is to develop operational criteria for standardized terminology and diagnostic criteria for pneumonia after stroke. For this analysis, they performed a systematic review of criteria used to define pneumonia occurring after stroke in published research studies. They then evaluated the heterogeneity in reported pneumonia occurrence, focusing on the studies that used standard criteria for diagnosis, which the authors defined as those who used existing published respiratory or other society diagnostic criteria.

Literature was reviewed for all studies of ischemic stroke, intracerebral hemorrhage, or both that reported occurrence of pneumonia and were published between January 2009 and March 2014. The final evaluation included 64 studies of 639953 patients. Standard criteria were used in 31% of studies, comprised of Centers of Disease Control and Prevention criteria (75%), MANN criteria (20%), and American Thoracic Society and Infectious Diseases Society of America criteria (5%). These criteria required various combinations of clinical, radiographic, and laboratory findings such as chest radiograph abnormality, fever, leukocytosis or leukopenia, abnormal respiratory examination, or hypoxia. An additional 41% used objective criteria for diagnosis that was not previously published.

The overall occurrence of pneumonia in this review was 14.3% (95% confidence interval, 13.2%–15.4%). This was higher than the 10% (95% confidence interval, 9%–10%) pneumonia occurrence reported in another systematic review of studies performed from 1950 to 2010. Reasons for the higher frequencies in the current review are unclear but may relate to the differences in time periods and inclusion criteria of the 2 systematic reviews. Surprisingly, the pneumonia occurrence in this review was higher in the subgroup of studies that used standard criteria for diagnosis (19.1%; 95% confidence interval, 15.1%–23.4%) compared with other diagnostic criteria, demonstrating that standard criteria were not any more stringent than other commonly used criteria.

Heterogeneity was measured using the $I^2$ statistic, which represents the percentage of variation across studies that is due to heterogeneity rather than chance. A value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity. As expected, there was substantial heterogeneity observed in occurrence of pneumonia across studies ($I^2=98.9$%). Interestingly, substantial heterogeneity was also observed among studies that used standard criteria ($I^2=98.5$%) and even within those that that used the same Centers for Disease Control and Prevention criteria. The heterogeneity observed was not explained by stratifying for potential confounders of age, stroke subtype, and time from stroke onset to recruitment.

The authors posit that these findings warrant the development of consensus-based, operational criteria for terminology and diagnostic approach to the spectrum of lower respiratory tract infection in stroke care. However, as the authors point out, it is difficult to know how much heterogeneity is from these marked differences in patient populations versus how much can be ascribed to variability in the definition of pneumonia that was used. The fact that studies that used the same definition still had significant heterogeneity suggests that there are additional factors apart from definition that are playing an important role. The function that pneumonia diagnosis played in the studies differed, ranging from its use as a predictor of stroke outcomes to being the focus of the study. Importantly, there were significant differences in the study design and populations included in the review. Studies enrolled patients at different time points in their stroke recovery and in various settings including stroke unit, medical wards, rehabilitation wards, and intensive care units. The setting was unclear in 28% of the studies. The studies followed patients for varying lengths of time, ranging from 5 days to 3 months. The diagnosis of pneumonia is more likely to occur in the first few days after stroke, and these factors could have affected the reporting of occurrence across studies. Stroke severity, which is a predictor of pneumonia, was reported in only 47% of studies. Because of missing data, the ability of the authors to determine the impact of these study differences on pneumonia diagnoses was limited.

It is worth mentioning that even randomized trials with well-accepted definitions of clinical events and relatively homogeneous study designs can have differences in event rates in the
control arms that are typically ascribed to the differences in patient characteristics.\textsuperscript{17\textendash}19 A standard definition for pneumonia that can be used in clinical research studies would indeed help better understand predictors of pneumonia and the effectiveness of different interventions, but as the authors have demonstrated, may not eliminate heterogeneity in pneumonia occurrence.

The use of a standard definition of pneumonia for use in the clinical management of patients is a question for empirical study. Diagnosing pneumonia in clinical practice can be challenging. The source of fever and leukocytosis is often unclear. The appearance of abnormalities on chest radiography can be delayed, and it can be difficult to differentiate between atelectasis, volume overload, and infiltrate. As a result, management of patients is often through a pragmatic approach. Broad spectrum antibiotics can be started even when the source of infection is unclear.\textsuperscript{15} A standard diagnosis of pneumonia may be more helpful in clinical care if it is accompanied by management recommendations for these different clinical scenarios and levels of probability.

This article highlights the range in reported occurrence of pneumonia after stroke. In addition to supporting the value of having a uniform definition for pneumonia in clinical research, it underscores the importance of including clinically relevant data such as stroke severity and study duration when reporting the study results. Development of an organized approach to evaluate pneumonia after stroke would be beneficial to all those studying and managing patients with stroke. We look forward to the results of the work done by the PISCES group.

Acknowledgments
Srividya Ramachandran, PhD, provided editorial assistance for this article.

Disclosures
None.

References
It Is Time to Attack Pneumonia Head-On
Irene L. Katzan

Stroke. 2015;46:1153-1154; originally published online April 9, 2015;
doi: 10.1161/STROKEAHA.115.009084
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2015 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://stroke.ahajournals.org/content/46/5/1153

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published
in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office.
Once the online version of the published article for which permission is being requested is located, click
Request Permissions in the middle column of the Web page under Services. Further information about this
process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/