

INTRODUCTION:

Wheeze is an important sign indicating a potentially severe adverse event in vaccine and drug trials, particularly in children. However, there are currently no consensus definitions of wheeze or associated respiratory compromise in randomized controlled trials (RCTs).

OBJECTIVE:

To identify definitions and severity grading scales of wheeze as an adverse event in vaccine and drug RCTs enrolling children <5 years and to determine their diagnostic performance based on sensitivity, specificity and inter-observer agreement.

METHODS:

We performed a systematic review of electronic databases and reference lists with restrictions for trial settings, English language and publication date ≥ 1970 . Wheeze definitions and severity grading were abstracted and ranked by a diagnostic certainty score based on sensitivity, specificity and inter-observer agreement.

RESULTS:

Of 1205 articles identified using our broad search terms, we identified 58 eligible trials conducted in 38 countries, mainly in high-income settings. Vaccines made up the majority (90%) of interventions, particularly influenza vaccines (65%). Only 15 trials provided explicit definitions of wheeze. Of 24 studies that described severity, 11 described wheeze severity in the context of an explicit wheeze definition. The remaining 13 studies described wheeze severity where wheeze was defined as part of a respiratory illness or a wheeze equivalent. Wheeze descriptions were elicited from caregiver reports (14%), physical examination by a health worker (45%) or a combination (41%). There were 21/58 studies in which wheeze definitions included combined caregiver report and healthcare worker assessment. The use of these two methods appeared to have the highest combined sensitivity and specificity.

CONCLUSION:

Standardized wheeze definitions and severity grading scales for use in pediatric vaccine or drug trials are lacking. Standardized definitions of wheeze are needed for assessment of possible adverse events as new vaccines and drugs are evaluated.