Drug Research and Development for Adults Across the Older Age Span

The COVID-19 Experience

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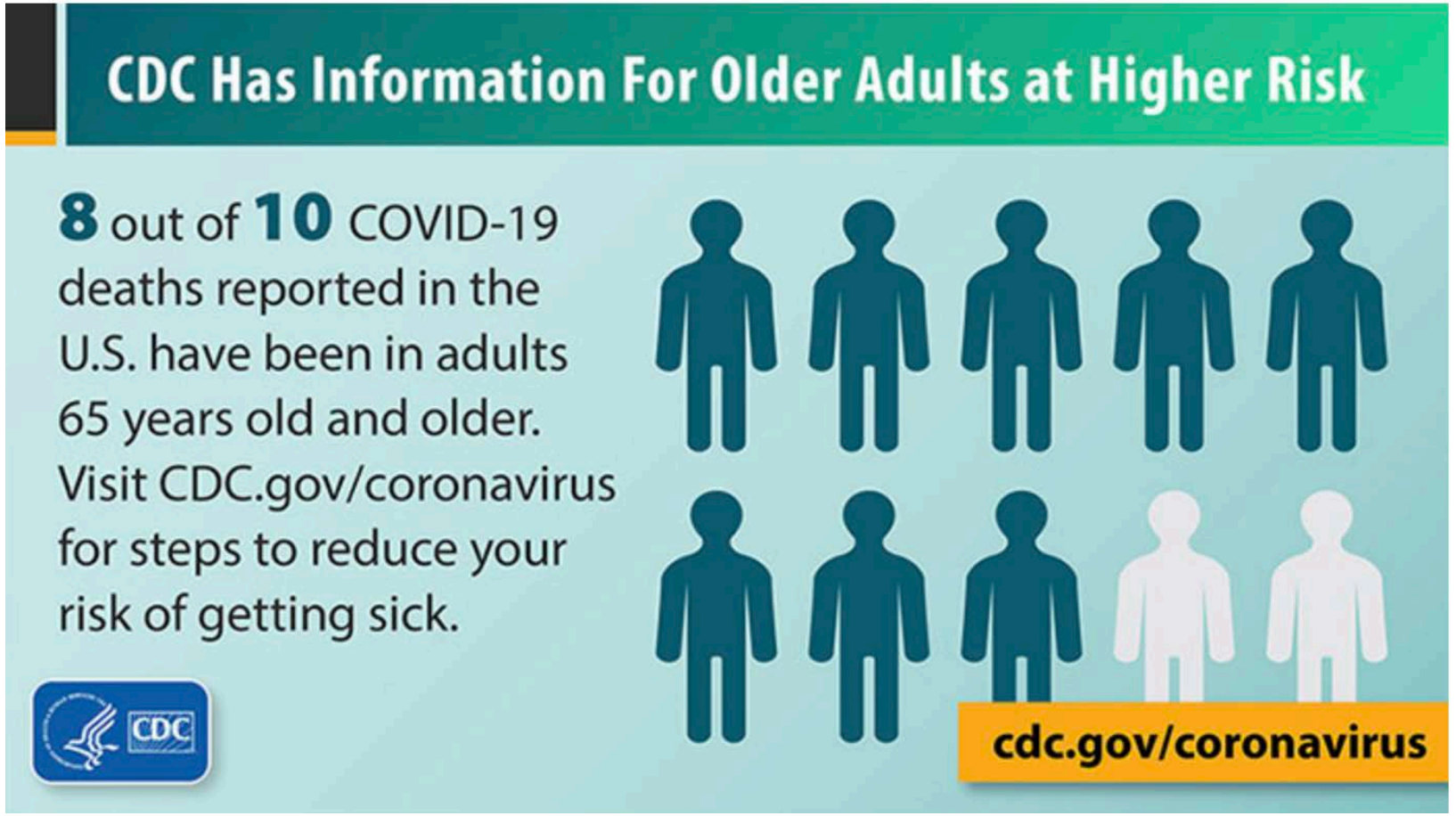
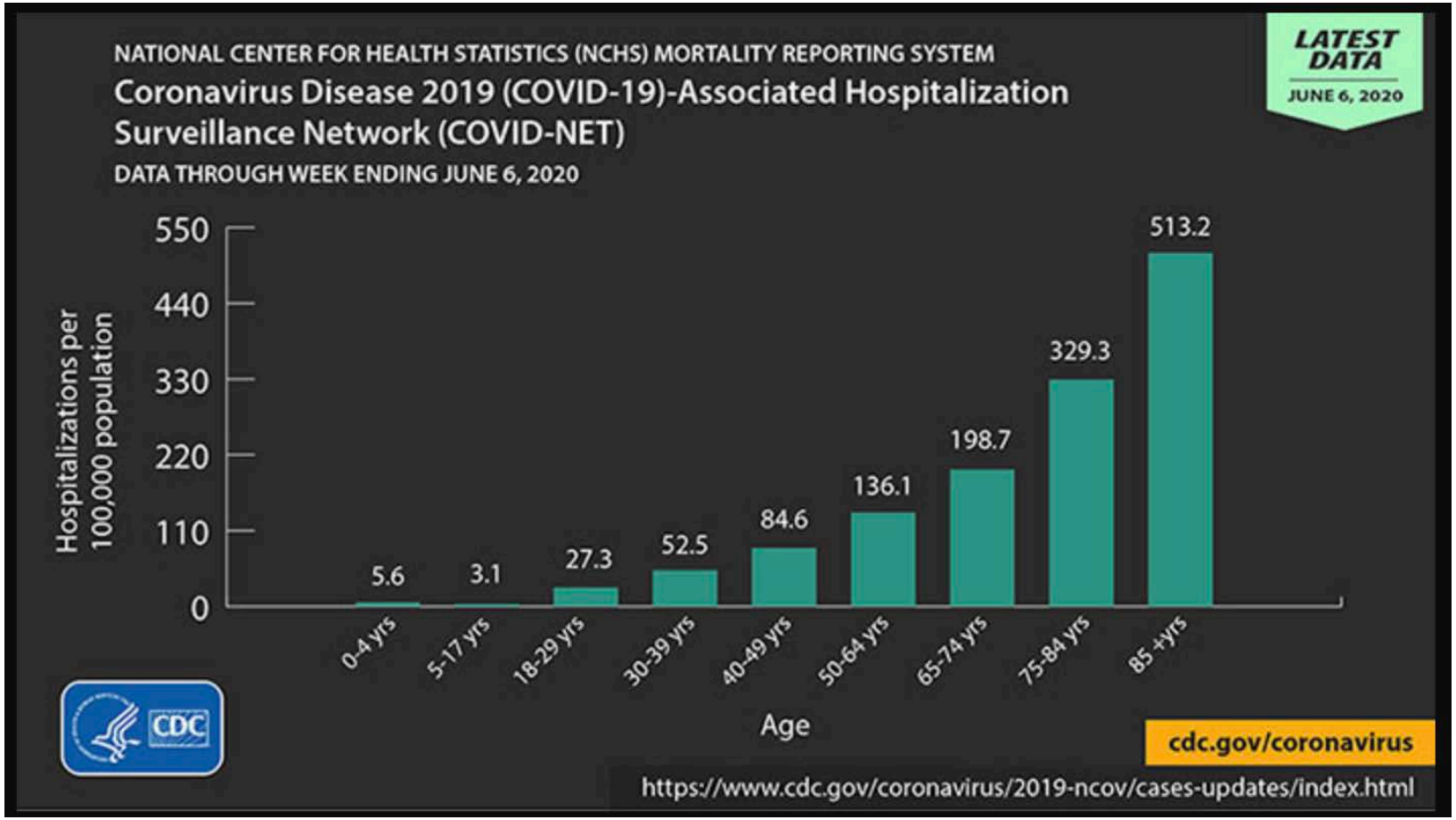
Infectious Diseases and Older Persons

- History of many common acute infectious diseases (pneumonia, urinary tract infections, influenza) show worse outcomes in older persons
  - Different in immune function and response
  - Different co-morbidities and co-medications
- Effects of interventions (drugs and vaccines) vary and differ in older persons compared to younger
- This experience being seen once again in COVID-19

COVID-19: Age and Outcomes



COVID-19: Age and Outcomes



Implications

- Implications for clinical trials and value based care
  - Inclusion and exclusion criteria for studies
  - Interventions in studies
  - Outcomes measured
  - Value for medical interventions – benefits and harms in those most

- Current initiatives:
  - Patient focused drug development
  - Real world evidence – how interventions will be used in practice

ID Trials

Clinical Infectious Diseases

MAJOR ARTICLE

Assessment of Data Supporting the Efficacy of New Antibiotics for Treating Infections Caused by Multidrug-resistant Bacteria

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Background. Infections caused by multidrug-resistant (MDR) bacteria are a major public health threat. We aimed to assess the data supporting US Food and Drug Administration (FDA) approval of new agents aimed to treat MDR bacterial infections and the data provided by postmarketing studies.

Methods. We identified all drugs with in vitro activity against MDR bacteria initially approved by the FDA between January 2010 and December 2018. Characteristics of trials supporting approval and regulatory pathways were collected from Drugs@FDA. Characteristics of postmarketing studies were extracted from drug labels and ClinicalTrials.gov entries effective 1 June 2019.

Results. Initial approval of 11 newly approved antibiotics with anti-MDR activity was supported by 20 trials, all with noninferiority design. All initially approved indications were for common infections, mostly acute bacterial skin and skin-structure infections, regardless of causative microorganism. The proportion of MDR bacteria in most trials was low (<10% for gram-negative infections, <1% for gram-positive pneumonia). Most trials (90%) excluded immunocompromised and critically ill patients. Of 16 additional postmarketing randomized controlled trials identified through ClinicalTrials.gov, only 2 exclusively included infections caused by MDR bacteria, comprising 116 patients. No drug was granted accelerated approval, which would mandate postmarketing efficacy studies.

Conclusions. The approval of new drugs with potential clinical activity against MDR bacteria is supported by trials evaluating infections caused by non-MDR organisms, using noninferiority design and excluding the patients most likely to require these agents. Subsequent postmarketing efficacy data against these organisms are scarce. Healthcare professionals and regulators should demand more robust data to support clinical decision making.

Keywords. FDA approval; novel antibiotics; multidrug resistant bacteria; clinical trials.

Example of Patient Reported Outcomes

- Outcomes that matter to patients – survival, function in daily life, symptoms
- Some outcomes known only to patients themselves (symptoms, function) and require asking patients to determine
- Patient Reported Outcomes - information gathered from patients without interpretation by anyone else
- *Direct* measures of patients health status (unlike clinician reported measures which are indirect observations)

Patient Reported Outcomes in Myelofibrosis

Table 1. Baseline Characteristics of the Patients.*

Variable	Ruxolitinib (N=155)	Placebo (N=154)
Median age (range) — yr	66 (43–91)	70 (40–86)
Male sex — % of patients	51.0	57.1
Myelofibrosis subtype — % of patients		
Primary myelofibrosis	45.2	54.5
Post–polycythemia vera myelofibrosis	32.3	30.5
Post–essential thrombocythemia myelofibrosis	22.6	14.3
IPSS risk status — % of patients		
High	58.1	64.3
Intermediate 2	41.3	35.1
Previous hydroxyurea use — % of patients	67.1	56.5
Median platelet count (range) — $\times 10^{-9}$/liter	262 (81–984)	238 (100–887)
Median hemoglobin (range) — g/liter	105 (66–170)	105 (35–173)
Median palpable spleen length (range) — cm	16 (0–33)†	16 (5–34)
Median spleen volume (range) — cm^3	2598 (478–7462)	2566 (521–8881)
JAK2 V617F–positive — % of patients	72.9	79.9

Patient Reported Outcomes in Infectious Diseases

Clinical Infectious Diseases

SUPPLEMENT ARTICLE

Patient-Reported Outcome Assessments as Endpoints in Studies in Infectious Diseases

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The goal of administering medical interventions is to help patients live longer or live better. In keeping with this goal, there has been increasing interest in taking the "voice" of the patient into account during the development process, specifically in the evaluation of treatment benefits of medical interventions, and use of patient-centered outcome data to justify reimbursement. Patient-reported outcomes (PROs) are outcome assessments (OAs) used to define endpoints that can provide direct evidence of treatment benefit on how patients feel or function. When PROs are appropriately developed, they can increase the efficiency and clinical relevance of clinical trials. Several PROs have been developed for OA in specific infectious diseases indications, and more are under development. PROs also hold promise for use in evaluating adherence, adverse effects, satisfaction with care, and routine clinical practice.

Keywords. infectious diseases; clinical trials; patient-reported outcomes; endpoints; clinical practice.

Patient Reported Outcomes in COVID-19

RESEARCH ARTICLE

Performance of the inFLUenza Patient-Reported Outcome (FLU-PRO) diary in patients with influenza-like illness (ILI)

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Abstract

Background

The inFLUenza Patient Reported Outcome (FLU-PRO) measure is a daily diary assessing signs/symptoms of influenza across six body systems: Nose, Throat, Eyes, Chest/Respiratory, Gastrointestinal, Body/Systemic, developed and tested in adults with influenza.

Objectives

This study tested the reliability, validity, and responsiveness of FLU-PRO scores in adults with influenza-like illness (ILI).

Challenges and Opportunities

- Prior beliefs that older persons can't answer questions regarding their own health-may be true in some cases but not in all (or most) persons
  - "Too sick" to answer questions
  - Dementia
  - "patient burden" – easy to answer; burden of blood draws, nasal swabs, etc.?
  - Leads to reliance on lab testing/ clinician outcomes instead of patient outcomes (Hey et al JAMA Internal Medicine 2019)
  - Assumptions in absence of evidence

- Prior belief that older persons cannot use electronic devices
  - Providing devices and training
  - Telephone administration
  - Site staff administration

Use of PROs in Older Persons with Infections

Patient-Reported Outcomes

Evaluation of Efficacy Endpoints for a Phase IIb Study of a Respiratory Syncytial Virus Vaccine in Older Adults Using Patient-Reported Outcomes With Laboratory Confirmation

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ABSTRACT

Objectives: There are no approved vaccines for respiratory syncytial virus (RSV), and consensus on methods to assess RSV vaccine efficacy has not been established. In this study of an adjuvanted RSV vaccine, we evaluated an RSV disease endpoint using a patient-reported outcome instrument (the inFLUenza Patient-Reported Outcome instrument [FLU-PRO]) and molecular testing for virologic confirmation.

Methods: In a randomized, blinded efficacy study (NCT02508194), 1900 adult participants aged ≥60 years who had any respiratory symptom lasting ≥24 hours recorded symptoms in a FLU-PRO–based workbook for 21 days, self-collected nasal swabs on illness days 2 to 4, and had a site-collected swab obtained on (approximately) day 4. The endpoint, acute RSV-associated respiratory illness (ARA-RI), required specific symptoms with virologic confirmation.

Results: The FLU-PRO demonstrated reliability, ability to detect change, and validity and had high participant adherence and acceptable patient burden in the setting of an RSV prevention trial. The ARA-RI endpoint definition captured all 33 virologically confirmed RSV illnesses for which symptom data were provided, and in 32 of these, at least 1 lower respiratory symptom was reported. Sensitivity analysis with an endpoint requiring ≥2 lower respiratory symptoms captured greater symptom severity but fewer cases. Results of self- and site-collected swabs were highly correlated. Self-swabbing detected 9 additional cases that would have been missed by site swabbing only.

Conclusions: These results demonstrated the reliability and validity of the ARA-RI definition and of the FLU-PRO for use in RSV studies. Self-swabbing improved RSV detection.

Keywords: microbiological confirmation, patient-reported outcomes, respiratory syncytial virus.

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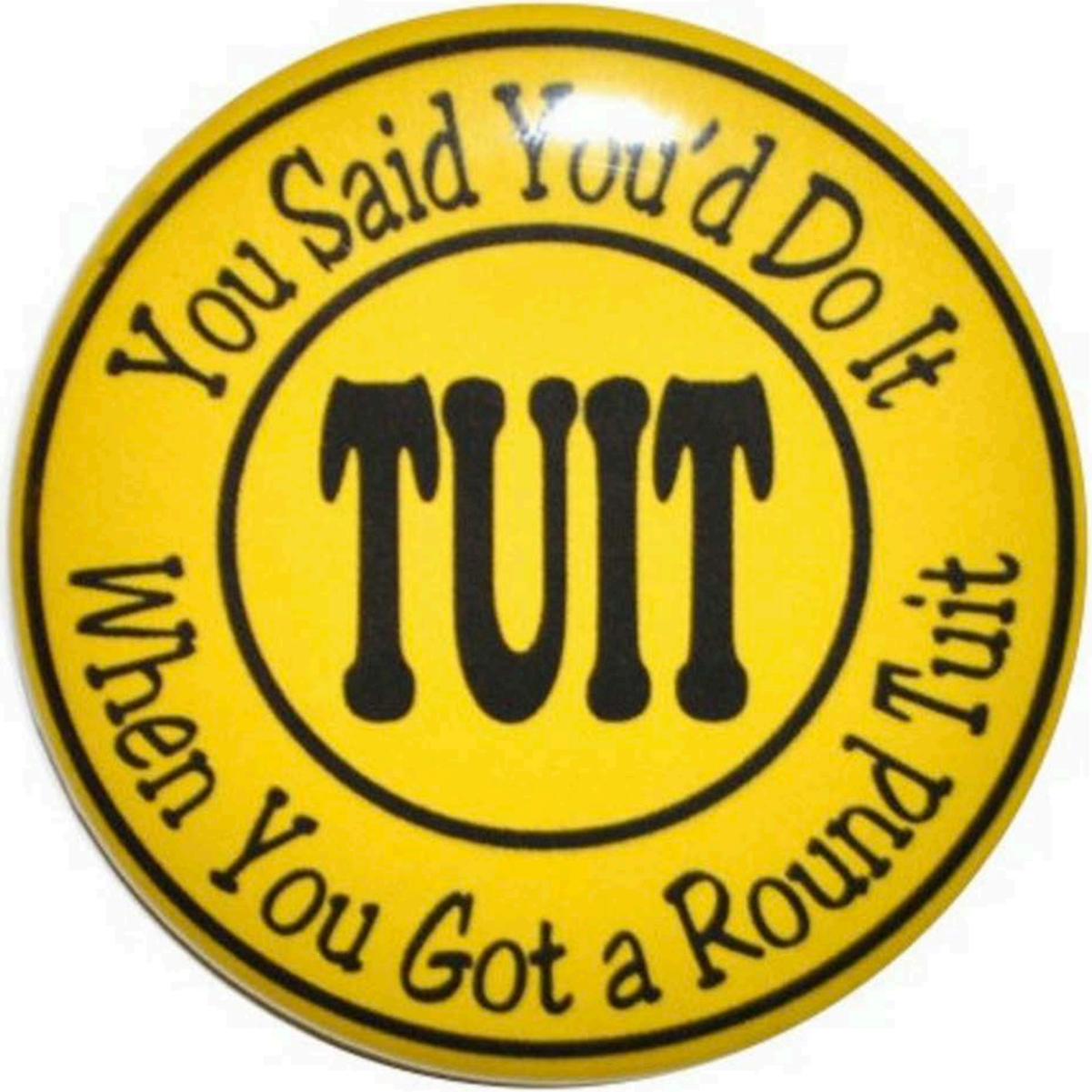
You Said You'd Do It
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When You Got a Round Tuit

Conclusions

- Many acute infections have greatest impact in older persons
- Need to *include* older persons in clinical studies to obtain better real-world evidence especially given potential differences in effectiveness and adverse effects
- Patient reported outcomes directly measure affect on patients lives
  - Can and should be used in infectious diseases
  - Can and should be used in older persons
- Better measurement of patient *outcomes* in those most affected results in better value care

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