

Enrollment of older adults in COVID-19 trials

Sharon K. Inouye, M.D., M.P.H.

Professor of Medicine

Beth Israel Deaconess Medical Center

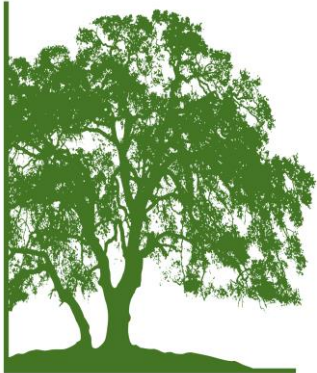
Harvard Medical School

Milton and Shirley F. Levy Family Chair

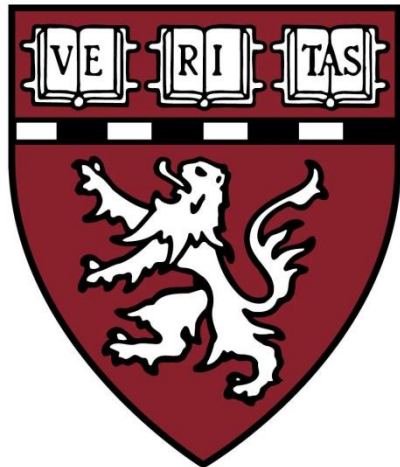
Director, Aging Brain Center

Hebrew SeniorLife

Hospital Elder Life Program



HELP



Disclaimer

- No conflicts of interest to disclose
- The views presented in this presentation represent the personal opinion of the speaker and do not reflect the official positions of the United States Food and Drug Administration (FDA).



Background

- Longstanding history of lack of inclusion of older adults in clinical trials
- Many recent calls and efforts for inclusion in clinical trials, including by the NIH (Inclusion Across the Lifespan Policy)
- Necessity for inclusion:
 - evaluation of efficacy and dosing adjustments
 - determining side effects and safety
 - assuring equitable access and insurance coverage for the treatment
- With Covid-19 pandemic and its over-riding predilection for serious disease and death in older adults as the key target population
 - Wanted to see if this would spur a change in inclusion of older adults in clinical trials



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The Exclusion of Older Persons From Vaccine and Treatment Trials for Coronavirus Disease 2019—Missing the Target

Benjamin K. I. Helfand, MSc^{1,2}; Margaret Webb, BA³; Sarah L. Gartaganis, MSW, MPH³; Lily Fuller, BA³; Churl-Su Kwon, MD, MPH⁴; Sharon K. Inouye, MD, MPH³

» [Author Affiliations](#) | [Article Information](#)

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Goals of the Study

- Examine all clinical trials for COVID-19 indexed in ClinicalTrials.gov from 10/1/19 to 6/1/20
- Review each study description for:
 - Inclusion and exclusion criteria for any specific age cut-offs
 - Other exclusionary criteria that might preferentially exclude older adults



Methods

- Age cut-offs:
 - Reviewed all portions of eligibility criteria: ages eligible for study, inclusion criteria, exclusion criteria
 - Any age exclusions of age 55 and older were noted
- Indirect age-related exclusions:
 - Reviewed all entries for indirect exclusions in pre-specified categories--
 - Broad, poorly justified exclusions (“any condition the study investigator considered ineligible for clinical trials”)
 - Specific comorbidities where severity or degree not specified (e.g., any hypertension, any diabetes, anemia non-specified)
 - Nonspecific “concerns about compliance”
 - Non-specified hearing or vision impairment
 - Requirement for use of information technology (e.g., internet, smartphone, texting, webcam)



Figure 1. Clinical Trial Selection Process

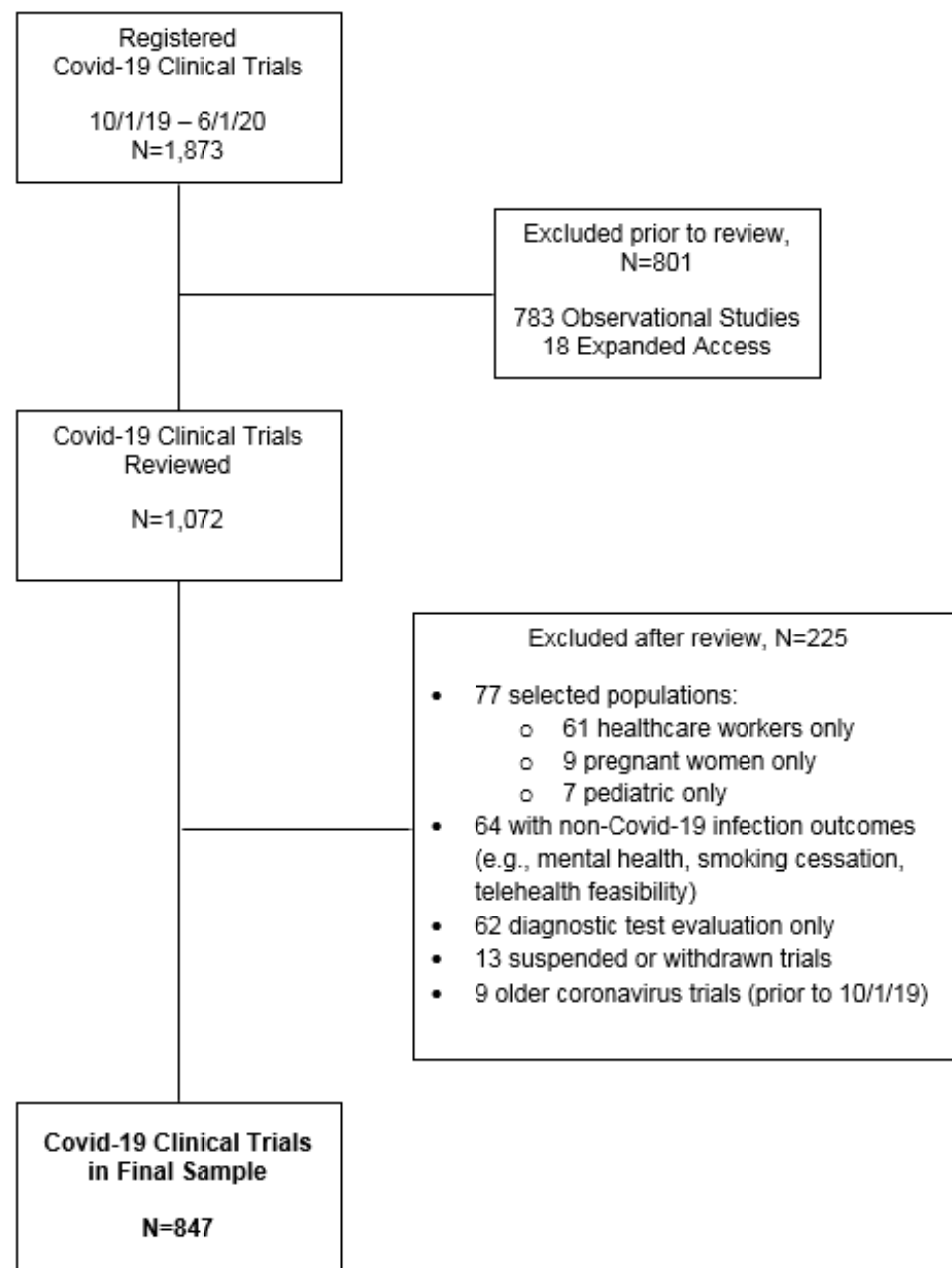


Table 2. Age-based exclusions by treatment type (N=847)

Treatment Type (n)	Age categories excluded						Total (%)*
	>55 or ≥55 v	>60 or ≥60 v	>65 or ≥65 v	>70 or ≥70 v	>75 or ≥75 v	>80 or ≥80 v	
Vaccine (18)	3	4	1		1	2	11 (61%)
Stem cells (38)		2	3	4	8	4	21 (55%)
Antiparasitic (14)		2	2	1	1		6 (43%)
Nutraceuticals, Vitamins & Minerals (53)	1	2	3	4	5	4	19 (36%)
Blood products (21)	1	1		1	1	2	6 (29%)
Oxygen (15)	1			1	1	1	4 (27%)
Antiviral (74)	5	1	2	1	5	5	19 (26%)
Hydroxychloroquine/ Chloroquine (60)	2	2		2	3	6	15 (25%)
Multimodal (48)			3	2	3	3	11 (23%)
Immunomodulatory (144)	1		4	3	7	18	33 (23%)
Antiseptic (10)				1		1	2 (20%)
Non-pharmacologic (45)	2	1	2	1	2	1	9 (20%)
Anticoagulant (29)				1	1	3	5 (17%)
Convalescent plasma (63)		2	1	2	1	4	10 (16%)
Antibiotic (26)	1				1	2	4 (15%)
Antihypertensive (26)		1				3	4 (15%)
Other drug treatments [†] (60)			2	2	1	2	7 (12%)
Nitrous Oxide (9)			1				1 (11%)
Anti-inflammatory (31)				1	1	1	3 (10%)
Device (32)			1		1	1	3 (9%)
Prone positioning (15)						1	1 (7%)
Steroid (16)						1	1 (6%)
Total All Trials (847)	17	18	25	27	43	65	195 (23%)
Phase III Total (232)	3	4	5	2	9	15	38 (16%)



Table 3. Indirect age-related exclusions by treatment type (N=847)

Treatment Type (n)	Broad, non-specified	Specific Comorbidities	Compliance Concerns	Requiring technology	Other Reasons	Any indirect age-related exclusion (one per study) [†]	Combined age and indirect exclusion [†]
Vaccine (18)	11	9	9	1	1	7 (39%)	18 (100%)
Stem cells (38)	18	1	15			9 (24%)	30 (79%)
Antiparasitic (14)	3	6	4			4 (29%)	10 (71%)
Nutraceuticals, Vitamins, Minerals (53)	10	4	9	3	2	13 (25%)	32 (60%)
Blood products (21)	3	2	4			8 (38%)	14 (67%)
Oxygen (15)	2	1	6	1	1	6 (40%)	10 (67%)
Antiviral (74)	22	8	20		2	22 (30%)	41 (55%)
Hydroxychloroquine/Chloroquine (60)	10	5	14	4	3	20 (33%)	35 (58%)
Multimodal (48)	13	4	11	1	1	14 (29%)	25 (52%)
Immunomodulatory (144)	35	5	33		2	43 (30%)	76 (53%)
Antiseptic (10)		2	2	1		4 (40%)	6 (60%)
Non-pharmacologic (45)	2	6	15	4	1	16 (36%)	25 (56%)
Anticoagulant (29)	5	2	5			10 (34%)	15 (52%)
Convalescent plasma (63)	7	1	11		1	11 (17%)	21 (33%)
Antibiotic (26)	4	3	6	2		8 (31%)	12 (46%)
Antihypertensive (26)	3	2	6	1		6 (23%)	10 (38%)
Other drug treatments* (60)	8	1	13			12 (20%)	19 (32%)
Nitrous Oxide (9)	4		4			5 (56%)	6 (67%)
Anti-inflammatory (31)	10	3	7	1		14 (45%)	17 (55%)
Device (32)	2	2	13	1	3	13 (41%)	16 (50%)
Prone positioning (15)		1	3	1		3 (20%)	4 (27%)
Steroid (16)	2		3			4 (25%)	5 (31%)
Total All Trials (847)	174	68	213	21	17	366 (43%)[†]	447 (53%)[†]
Studies without age exclusion (652)	119	31	157	16	12	252 (39%) [†]	---
Phase III Total (232)	48	12	52	2	4	100 (43%) [†]	115 (50%) [†]
Studies without age exclusion (194)	38	6	42	1	4	77 (40%) [†]	---



Study conclusions

- Our study raised concerns that older adults are highly likely to be excluded from COVID-19 related treatment trials
 - Same findings applied to Phase III clinical trials (intended to enroll broad target populations)
 - Particularly likely to be excluded from planned vaccine trials
- Exclusions include both age-related cut-offs and indirect exclusions preferentially affecting older adults
- Some exclusions for severe or uncontrolled comorbidities may be needed to protect the health and safety of older adults
- Caution must be taken to avoid unnecessary exclusions of older adults for reasons (e.g., expediency) that are not well-justified



Did the predictions hold true?

- After sounded the alarm, wanted to examine enrollment of older adults into COVID-19 vaccine trials
 - Essential to assess efficacy, need for dosage adjustment, immune response
 - Critical to assess adverse effects in the target population
- Examined published studies of 4 vaccines for SARS-CoV-2
 - Determined inclusion of patients age 65+
 - Specifically examined total numbers in the 75+ age group
 - Examined inclusion of older adults 65+ with comorbidities, who would be representative of the general older population
 - Examined whether any long-term care patients included



AstraZeneca/Oxford (ChAdOx1 nCoV-19)

[Voysey M et al. Lancet. 12/8/2020]

- Total N = 11,636
- Inclusion of older adults:
 - 56-69 yo, n=974 (8%)
 - 70+, n=444 (4%)
- Included patients with comorbidities (lung, cardiac, obesity, DM)
 - No comorbidities reported by age group; not clear whether there were older adults with comorbidities
- Nursing home: None included



Pfizer (BNT162b2)

[Polack F et al., NEJM. 12/10/20]

- Total N = 43,448
- Inclusion of older adults:
 - 65-75 yo, n=8613 (21%)
 - 75+, n=1712 (4%)
- Included patients with comorbidities (HTN, DM, other)
 - 65-75 yo, n=2263 (5%) had 1+ comorbidity
 - 75+, n=725 (2%) had 1+ comorbidity
- Nursing home: None included



Moderna (mRNA-1273)

[Baden LR et al., NEJM. 12/30/20]

- Total N = 30,420
- Inclusion of older adults:
 - 65-74 yo, n=5727 (21%)
 - 75+, n=1299 (5%)
- Included patients with comorbidities (lung, cardiac, obesity, DM)
 - No comorbidities reported by age group; not clear whether there were older adults with comorbidities
- Nursing home: None included



Sputnik V (Gam-COVID-Vac)

[Logunov DY et al., Lancet. 2/2/2021]

- Total N = 21,862
- Inclusion of older adults:
 - 60-69 yo, n=1774 (8%)
 - 70-79 yo, n=336 (2%)
 - 80+, n=34 (0.2%)
- Included patients with comorbidities (HTN, cardiac, obesity, DM)
 - 47% of those age 60+ had at least 1 comorbidity
- Nursing home: None included



Across all COVID-19 vaccine trials

- Only a few thousand older adults (70+) have been included to date
 - Very few with comorbidities
 - None yet in nursing home population
- Vaccine efficacy still demonstrated in the older populations included
- Raises concerns about generalizability of trial results to entire older population in terms of efficacy and safety
- To assure applicability and relevance of clinical trial results, must find ways to include the older population in adequate representation with which they are affected by the disease in question.



Barriers to enrollment of older adults

- Logistic constraints
- Concerns about safety (beware paternalism)
- Expediency/speed of trial completion
- Financial considerations
- Hesitancy of study population

