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A cross-sectional study of participant recruitment rates in published phase III influenza therapeutic randomized controlled trials conducted in the clinical setting☆

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ABSTRACT

Objective: A recent academic-government partnership demonstrated the feasibility of utilizing Emergency Departments (ED) as a primary site for subject enrollment in clinical trials and achieved high rates of recruitment in two U.S. EDs. Given the ongoing need to test new therapeutics for influenza and other emerging infections, we sought to describe the historical rates of participant recruitment into influenza Phase III therapeutic RCTs in various clinical venues, including EDs.

Study design: A cross-sectional study was performed of influenza therapeutic Phase III RCTs published in PubMed, Embase, Scopus, and Clinicaltrials.gov from January 2000 to June 2019.

Main outcome: To estimate the weighted-average number of influenza-positive participants enrolled per site per season in influenza therapeutic RCT conducted in clinical settings, and to describe basic trial site characteristics.

Results: 47 (0.7%) of 7008 articles were included for review of which 43 of 47 (91%) included information regarding enrollment sites; of these, 2 (5%) recruited exclusively from EDs with the remainder recruiting from mixed clinical settings (inpatient, outpatient, and ED). The median enrollment per study was 326 (IQR: 110, 502.5) with a median of 11 sites per study (IQR: 2, 59.5). Included studies reported a median of 201 (IQR: 74, 344.5) confirmed influenza-positive participants per study. The pooled number of participants enrolled per site per season was 11 (95% CI: 10, 12). The pooled enrollment numbers per clinical site after excluding the two 'ED only recruitment' studies were less [10.7 (95% CI: 9.9, 11.6)] than the pooled enrollment numbers per clinical site for the two 'ED only recruitment' studies [89.5 (95% CI 89.2–89.27)].

Conclusion and relevance: Published RCTs evaluating influenza therapeutics in clinical settings recruit participants from multiple sites but enroll relatively few participants, per site, per season. The few ED-based studies reported recruited more subjects per site per season. Untapped opportunities likely exist for EDs to participate and/or lead therapeutic RCTs for influenza or other emerging respiratory pathogens.

1. Introduction

1.1. Background

Seasonal influenza accounts for an estimated 290,000 to 650,000 deaths annually [1]. Despite efforts to produce a targeted vaccine, the effectiveness of seasonal influenza vaccine has ranged from 19% to 60% over the last decade amongst recipients in the United States [2,3]. Given less than ideal efficacy of vaccines, there exists an ongoing need for development and evaluation of targeted therapeutics for influenza, to prevent and treat complications. The same holds true for current and future planning and response to respiratory virus epidemic and

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pandemics, such as Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Approval from the Food and Drug Administration (FDA) is required for the use of therapeutics for treatment of respiratory viral illness, including influenza. The process for approval can be lengthy, culminating in Phase III randomized controlled trials (RCTs) to demonstrate efficacy (superiority, non-inferiority, or equivalence). Currently, several neuraminidase inhibitors (e.g. oseltamivir, peramivir, and zanamivir) and polymerase acidic protein inhibitors (baloxavir) are FDA approved for influenza treatment [4]. Challenges remains, however, with regard to optimizing the operations of Phase III RCTs for seasonal and pandemic viral respiratory illnesses. Amongst these are the time, efforts and costs required to set-up and administer clinical trials (particularly multicenter and multi-national trials), the potential for emergence of viral resistance associated with the therapeutic agent under investigation, and the varied severity of illness amongst patients and seasons, which may require testing of the antiviral for specific indications [5,6]. Clinical trialists and government sponsors have also reported difficulties with recruitment of adequate numbers of participants, as a major barrier [7,8]. A potential untapped resource for improving clinical trial recruitment is emergency departments (ED).

1.2. Importance

Each year, EDs evaluate and care for a substantial proportion of all U.S. patients with influenza-like illness (ILI) who have acute respiratory infections, a subset of whom are ultimately diagnosed with influenza [9,10]. Historically, EDs have been under-utilized as a primary clinical venue for recruitment and enrollment of patients into RCTs designed to evaluate new influenza therapeutics, despite the fact that they represent the front lines of our health care setting for both diagnosis and treatment [7]. Recently, an academic-government partnership was commissioned by the Biomedical Advance Research and Development Authority (BARDA) with the expressed purpose of assessing the feasibility of utilizing EDs as a primary site for subject enrollment in clinical trials; that study evaluated as a prototype, rates of recruitment as well as clinical outcomes of subjects treated with one of the newer influenza agent (intravenous peramivir), in comparison with those treated with oral oseltamivir, providing pilot data for future clinical trial design and planning [11]. Results from that study demonstrated comparable clinical outcomes, as well as the ability to achieve high rates of patient recruitment in two U.S. EDs, with an average of 60 patients enrolled per ED, per season (or a total of 179 subjects enrolled with site 1 enrolling for 2 consecutive seasons, and site 2 enrolling for 1 season) [12].

1.3. Goals of this investigation

Given this background, we conducted a cross-sectional analysis of the literature to ascertain the historical rates of patient recruitment into published influenza therapeutic RCTs in varied clinical settings, describing basic trial site characteristics, and compare findings with what was reported from the recent BARDA sponsored ED-initiated influenza RCT described above [11].

2. Methods

2.1. Study design

A cross-sectional analysis of published Phase III influenza therapeutic RCTs published in PubMed, Embase, Scopus, and Clinicaltrials.gov was conducted in accordance with Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines [13]. Inclusion criteria was restricted to human RCTs reported in the published literature from January 2000 to June 2019, in which enrolled subjects were tested and confirmed to have influenza. There was no restriction on participant age, sex, or health status. Studies that were not randomized controlled clinical trials were excluded.

2.2. Literature search

A search construct to capture influenza therapeutic RCTs was developed with the aid of a medical research librarian. The complete search strategy detailed in supplementary document was applied to Pubmed, Embase, Scopus, and Clinicaltrials.gov.

2.3. Study selection

Two authors (M.Y. and N.P.) independently applied the inclusion criteria to all identified and retrieved articles (Fig. 1, Flow diagram). A third person (Y–H.H.), an experienced infectious disease epidemiologist, supervised the procedure and resolved any disagreements via discussion serving as a tie-breaker to achieve consensus.

2.4. Data extraction

A structured data extraction tool was used to collect study characteristics. The authors (M.Y. and N.P.) who reviewed the articles extracted data from all included publications independently. Results were compared and differences were resolved by consensus, as described above. The following characteristics were extracted from all included studies: author, publication year, location of study, clinical setting type (outpatient or inpatient), primary outcome, study duration, number of influenza seasons included in the study, age range of the study population, numbers of participants randomized, numbers of participants with a confirmed influenza test, and whether or not an ED was included as a site of recruitment for study participants, as determined by a systematic search for the term emergency room or ED in the text of the Methods. Lack of information was recorded and used for the assessment for risk of biases.

2.5. Outcomes

The primary outcome of this study was to estimate the weighted average number of influenza-positive participants enrolled per site per season in Phase III influenza therapeutic RCT conducted in clinical settings, and to describe basic trial site characteristics. Basic trial site characteristics included clinical setting (e.g., inpatient, outpatient, ED), duration of the study, number of study site, participant's age range, number of participants randomized, number of participants with confirmed influenza, and therapeutics studied.

2.6. Statistical analysis

Data extracted from included studies were described using descriptive statistics. The overall pooled number of participants enrolled per site per influenza season and the corresponding 95% confidence intervals (CI) were calculated use a meta-analytic estimate with random effects model as described by Neyeloff and colleagues for Microsoft Excel v16 [14]. A DerSimonian and Laird random-effects model was used with the assumption there exists high variability in sampling errors and study populations across included studies [15]. Heterogeneity was assessed for pooled estimates using the Cochran's Q and I^2 statistics. Sensitivity analysis was performed on sites that did not use ED use the sole participant enrollment site.

3. Results

3.1. Study screening and selection

Overall, 7008 unique articles were identified from the initial search of 7384 articles after removal of duplicates (Fig. 1). Title and abstract

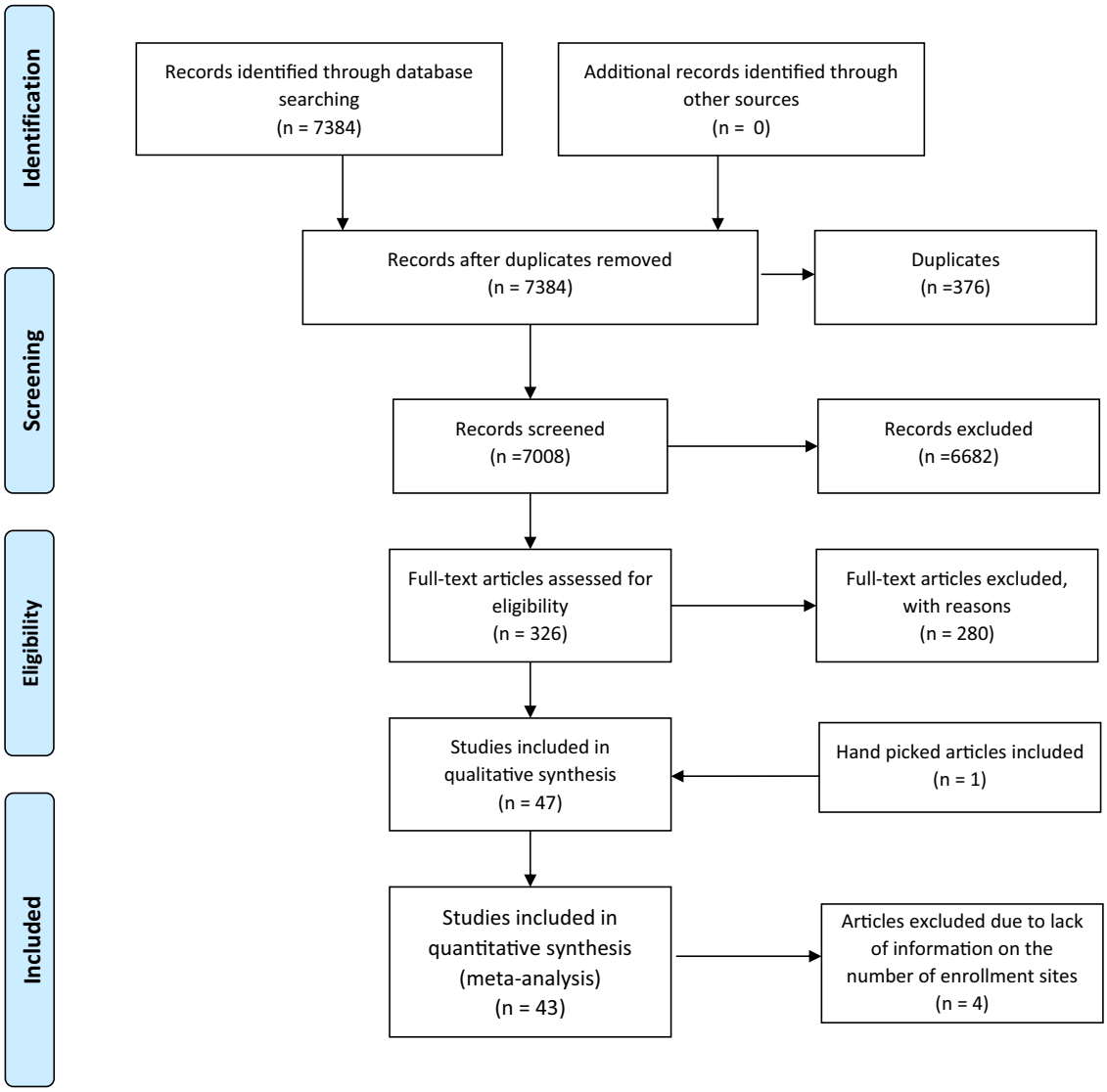

Fig. 1. Flow Diagram.

screening identified 326 articles (4.6%) that met inclusion criteria of which 47 articles (14.4%) fully met eligibility criteria and were included for review.

3.2. Study characteristics

The majority of included RCT studies enrolled participants in Asia (47%), followed by Americas (17%), multi-continental (19%), Europe (13%), and Oceania (4%). Clinical enrollment sites included outpatient (12 studies), inpatient (14 studies), inpatient and outpatient (5 studies), undisclosed (14 studies), ED and outpatient (1 study), and the ED only (2 studies). On average, each study enrolled participants throughout 1.5 (median: 1; IQR 1, 2) influenza seasons with one study taking place over 4 influenza seasons. The vast majority of studies (81%) enrolled participants across multiple sites rather than utilizing a single enrollment location. The average number of participants per study was 365 (median: 326; IQR: 110, 502.5, Range: 21, 1138), and the average number of sites per study was 41 (median: 11; IQR: 2, 59.5, Range: 1, 323). The average number of confirmed influenza positive participants per study was 256 (median: 201; IQR: 74, 344.5, Range: 21, 1099).

The 3 studies that included ED patients were all conducted outside the United States. In the 1 mixed study (ED and outpatient recruitment), Dixit et al. [16] carried out a multicenter RCT over one season in Australia utilizing both a pediatric ED and an outpatient family practice location to recruit enrolling 52 participants with confirmed influenza. The two ED only studies included (1) a multicenter single season RCT conducted in China with 8 different EDs, and recruited 480 adult patients, of which 225 patients had confirmed influenza; and; (2) a multicenter RCT over one season conducted in El Salvador and Panama utilizing 5 different EDs with 683 pediatric patients recruited, of which only 30 were confirmed to have influenza.

3.3. Treatment and outcomes

The most frequently studied therapeutics were the antivirals oseltamivir (51%), followed by zanamivir (18%), peramivir (12%), and laninamivir (9%), followed by 10% other agents (including herbal supplements, and varied experimental therapeutics). Most of the studies assessing the newer antivirals were direct head-to-head comparisons with oseltamivir, given that oseltamivir is often regarded as the standard of care comparator (Table 1). The majority of published studies ($n = 38$, 80.8%) reported favorable outcomes.

3.4. Weighted-average patient enrollment in influenza therapeutic RCTs

Four studies that did not provide exact number of sites for participant enrollment were excluded from the analysis ($n = 43$). The number of influenza confirmed positive participants enrolled in influenza RCTs ranged from 21 to 1099. The number of influenza positive participants enrolled per site per season ranged from 0.3 to 112. The weighted-average of participants enrolled per clinical enrollment site per influenza season was 11.0 (95% CI: 10.2, 11.8; Cochran's Q: 8546.6; I^2: 99.5) (Fig. 2). The average enrollment numbers per clinical site was similar, after excluding the two 'ED only recruitment' studies [10.7 (95% CI: 9.9, 11.6)]. The average enrollment numbers per clinical site for the two 'ED only recruitment' studies was 89.5 95% CI 89.2–89.27).

4. Discussion

In this study of Phase III RCTs, we found that the majority of studies evaluating influenza therapeutic agents were conducted either in Asia and the Americas, or were multicontinental. For RCTs that disclosed recruitment site locations, there was approximately an equal distribution of participant recruitment from outpatient and inpatient settings. The most frequently studied therapeutic agent was oseltamivir. Our study found very few RCTs (3/47) reported using the ED as a recruitment site. Notably, we found that the vast majority of published RCT studies included a large number of sites, with an average of 41 sites per study. However, there were relatively few subjects enrolled per site (pooled average number of participants enrolled per site, per influenza season was 11).

These findings, placed in the context of our recent ED-based influenza therapeutic RCT, where we achieved relatively high recruitment rates (60 participants per season per site) [12], suggest that EDs represent a potential, but as yet relatively untapped clinical venue for future recruitment and enrollment of participants into clinical trials for evaluation of therapeutics against influenza (and other respiratory viruses). The advantages and limitations of using the ED as a clinical site for recruitment into infectious disease therapeutic RCTs are discussed below.

Intuitively, therapeutics should be tested in the clinical setting in which they are likely to be used and amongst patients who are most likely to benefit from these interventions. EDs are responsible for a significant proportion of all patient visits annually across the United States [17-20]. Those EDs which are situated in large academic centers and located in high density catchment areas, and care for very high numbers of patients, with many seeing over 100,000 patients annually [21]. EDs also represent a primary clinical site for patients presenting with ILI, who are often significantly more sick and with more comorbid conditions compared to patients presenting to outpatient clinics [9,10]. Most recently during the coronavirus disease 2019 (COVID-19) pandemic, EDs have been reported to be responsible for a significant proportion of outpatient clinical visits for patients presenting with signs and symptoms consistent with COVID-19, for diagnosing those with confirmed COVID-19, and serving as the most frequent site for initial evaluation of patients, prior to hospital admission [22]. As the proverbial 'front door' to hospitals, and the aforementioned high annual volume of patient encounters, EDs thus represent a potential valuable recruitment site (in terms of patient's with the target disease) for clinical trials.

The recent expansion of ED research networks provides additional evidence and the foundation for an evolving role of ED in clinic trials research. Some well-known ED Networks include Pediatric Emergency Care Applied Research Network (PECARN) [23], EmeRgENcy Care Clinical Trials Network (SIREN) [24], and EMERGEncy ID NET, the later principally focused on infectious disease surveillance [25]. EMERGEncy ID NET a national, CDC (Centers for Disease Control and Prevention) network of academic EDs studying infectious diseases in patients seen in the ED, also has served as organizational network for the conduct of therapeutic RCTs; the "STOP-MRSA" trial as examples was led by core participating sites in the EMERGency ID group, with findings published in *The New England Journal of Medicine* [26]. Another recently formed trials network, which was advanced as an ED-ICU collaborative, conducted one of the largest trials to date, to test the role of a novel therapeutic cocktail for treating sepsis, with findings published in *JAMA* [27]. Notably, that study was successfully organized, implemented and completed in less than two years.

While EDs represent a substantial portion of total annual patient encounters nationally, conducting clinical trials in EDs is associated with unique challenges, including ED overcrowding and long wait times, the unpredictable nature of the ED course for any given patient, as well as limited resources and time for ED staff to engage in research during shift. Challenges also exist with regard to retention, given the episodic nature of care [28-33], with the potential of increased risk of subjects being "lost to follow-up" as compared to trials initiated in the outpatient or inpatient clinical setting, where additional time is available [34]. Given that EDs are largely regarded as the "safety net" of the U.S. healthcare system and are responsible for a substantial proportion of uninsured and underinsured patient encounters, these challenges have and may continue to represents a potential threat to conducting RCTs in EDs [35-37].

These issues can be largely mitigated by conducting research through well-funded ED Networks that have the support staff, infrastructure, and *experience* to conduct ED-based clinical trials. The numerous RCTs published by PECARN, EMERGEncy ID NET, and SIREN suggest that RCTs conducted in settings with established research infrastructure do not suffer from significant attrition for either patients discharged from the ED or admitted to the hospital. Furthermore, inclusion of EDs for patient recruitment provides an increased opportunity to improve engagement with minority and/or other marginalized populations, who have historically been underrepresented in clinical trials [38]. For EDs without established research teams or those who are not associated with ED Networks, financing such teams may be difficult and remains a potential barrier to ensuring diversity of clinical enrollment sites beyond academic health systems.

5. Limitations

There are a few limitations to this study that are worth noting. We found a paucity of influenza trials that reported utilizing the ED as a clinical enrollment site but some of the methods section of the studies did not fully detail the specific characteristics regarding exactly where recruitment, consent, enrollment and randomization occurred (beyond inpatient and outpatient). Nevertheless, based on the known historical limitations of confirming influenza positivity during the ED encounter (based on limitation of prior diagnostic assay), and the information we could glean from the methods section, it is highly likely that EDs have historically been under-utilized as primary source for subject recruitment and enrollment. Additionally, a number of the trials included this study required relatively small sample size needs to determine efficacy, and multicenter studies often specifically focus on achieving geographic representativeness (rather than high number of patients per site). Accordingly, our analysis does not truly capture the overall capacity of individual sites to have enrolled larger numbers of patients. Further, some trials (e.g. those therapeutic studies that are focused on patients with higher disease severity) had stringent inclusion and exclusion criteria. This heterogeneity across therapeutic influenza RCTs influences the findings reported here. Finally, while the Hsieh et al study sponsored by BARDA enrolled relatively high numbers of patients per site, that trial evaluated a relatively simple to test therapeutic agent (peramivir) for uncomplicated influenza and was designed in part, to explicitly test EDs ability to enroll patients in a clinical trial [12]. Additional direct experience engaging ED trialists will be required to assess the true opportunities associated with increased engagement of EDs across the range of therapeutic agents of interest.

Table 1
Description of included studies

First author & year	Setting	Age range	Setting	Sites	Participants randomized	Confirmed influenza	Study duration	Treatment used	Outcome
Hedrick JA 2000[39]	US, Canada, Europe, Israel	5–12	Outpatient	67	471	346	01/11/ 1999–04/19/1999	Zanamivir or placebo	Zanamivir was effective in shortening the duration and severity of influenza symptoms
Nicholson KG 2000[40]	Europe, China, Canada	≥18	Undisclosed	63	726	475	01/1998–03/1998	Oseltamivir or placebo	Oseltamivir was effective and well tolerated in the treatment of natural influenza in adults
Treanor JJ 2000[41]	USA	18–65	Inpatient/ Outpatient	60	629	374	01/1998–03/1998	Oseltamivir or placebo	Oseltamivir reduces the duration and severity of acute influenza in healthy adults
Aoki FY 2000[42]	Europe, USA	≥13	Undisclosed	14	722	722	Winter of 1995 and 1996	Zanamivir or placebo	Zanamivir treatment reduced absenteeism, improved patient productivity and well-being, and reduced the additional use of healthcare resources
Murphy KR 2000[43]	International	≥12	Undisclosed	159	525	313	04/25/1998–02/19/2000	Zanamivir or placebo	Zanamivir is an effective treatment for influenza in patients with asthma or COPD
Makela MJ 2000[44]	11 European countries	≥12	Outpatient	42	356	277	Winter of 1997 and 1998	Zanamivir or placebo	Zanamivir is effective in reducing the duration and severity of influenza illness and is well tolerated
Kaiser L 2000*[45]	Europe and North America	13–77	Undisclosed	Multi	575	N/A	11/1995–03/1996	Zanamivir or placebo	Zanamivir is effective and well tolerated
Boivin G 2000	Canada	≥12	Undisclosed	2	35	27	1997–1998	Zanamivir or placebo	Zanamivir reduces viral titers greater than the placebo
Whitley RJ 2001[46]	USA	1–12	Undisclosed	80	698	452	Influenza season 1998 to 1999	Oseltamivir or placebo	Oseltamivir administration is an efficacious and well-tolerated therapy for influenza in children when given 48 h of onset of illness
Martin C 2001*[48]	UK, Switzerland	13–97	Undisclosed	Multi	1138	N/A	Undisclosed	Oseltamivir or placebo	Oseltamivir is effective and well tolerated in high-risk patients with influenza
Li L. 2003[49]	China	18–65	Undisclosed	7	478	273	01/2001–04/2001	Oseltamivir or placebo	Oseltamivir was effective and well tolerated as treatment
Johnston SL 2005*[50]	International	6–12	Inpatient	Multi	335	N/A	1998 to 1999 (2 influenza seasons in northern and southern hemispheres)	Oseltamivir or placebo	Oseltamivir is effective and well tolerated in asthmatic children
Lin J 2006[51]	China	≥18	Inpatient/ Outpatient	9	118	56	2002–2003	Oseltamivir or SOC	Oseltamivir was effective and well tolerated as treatment
Sugaya N 2010[52]	Japan	≤9	Inpatient/ Outpatient	43	186	182	12/2008–03/2009	Laninamivir or Oseltamivir	Laninamivir octaonate was effective and well tolerated drug for treatment of children with oseltamivir-resistant H1N1
Wang L 2010[53]	China	18–65	Undisclosed (ED)	8	480	225	01/2007–06/2007	Antiwei or placebo	Antiwei was effective and well tolerated in treatment of natural influenza infection in adults
Watanabe A 2010[54]	Japan, Taiwan, Korea, Hong-Kong	≥20	Undisclosed	117	1003	977	11/2008–03/2009	Laninamivir or Oseltamivir	Single inhalation of Laninamivir octaonate is effective for the treatment of seasonal influenza
Duval X 2010[55]	France	≥18	Outpatient	19	541	447	01/07/2009–03/15/2009	Oseltamivir or Zanamivir	Oseltamivir-Zanamivir combination appeared less effective than Oseltamivir monotherapy and not significantly more effective than Zanamivir monotherapy
Heinonen S 2010[56]	Finland	1–3	Outpatient	1	409	98	2007 to 2009	Oseltamivir or placebo	Oseltamivir treatment started within 24 h of symptom onset provides substantial benefits to children with influenza A infection
Kohno S 2010[57]	Japan	20–64	Inpatient	75	300	299	12/2007–04/2008	Peramivir or placebo	Single IV dose of Peramivir is effective and well tolerated
Wang C 2011[58]	China	15–69	Inpatient	11	410	410	07/2009–11/2009	Oseltamivir or Maxingshigan--yinqiaosan (MY)	Oseltamivir and MY alone and in combination reduced time to fever resolution in patients with H1N1.
Kohno S 2011[59]	Japan, South Korea, Taiwan	≥20	Inpatient	146	1099	1099	11/2008–04/2009	Peramivir or Oseltamivir	Single IV Peramivir may be an alternative to a 5 day oral dose of Oseltamivir
Duan Z.P 2011[60]	China	16–65	Undisclosed	8	256	244	10/242009–11/23/2009	Lianhuaqingwen capsule or Oseltamivir	LHC achieved similar therapeutic effectiveness
Nabeshima S 2012[61]	Japan	20–64	Outpatient	1	33	33	01/2009–05/2009	Maoto, Oseltamivir, Zanamivir	Oral maoto granules in healthy adults with influenza was well tolerated and associated with equivalent clinical and virological efficacy to neuraminidase inhibitors
Dharan N.J 2012[62]	USA	1–79	Outpatient	1	21	21	01/19/2009–02/11/2009	Oseltamivir or placebo	Benefits were observed in early treatment group but small sample size

Katsumi Y 2012[63]	Japan	≤ 15	Inpatient	1	112	112	01/2011–05/2011	Laninamivir, Zanamivir	Efficiency and safety of Laninamivir and Zanamivir are the same
Watanabe A 2013[64]	Japan	≥20	Undisclosed	53	203	201	11/2009–03/2011	Laninamivir or Oseltamivir	Single inhalation of Laninamivir octaonate is effective for the treatment of seasonal influenza
Lee N 2013[65]	Hong-Kong	≥18	Inpatient	2	157	50	01/2010–06/2012	Oseltamivir	No additional benefit of higher-dose Oseltamivir treatment
Durigon EL 2013[66]	Brazil	≥ 5	Undisclosed	2	37	37	04/2009–08/2010	Oseltamivir	Standard and double dose Oseltamivir were well tolerated
South East Asia Infectious Disease Clinical Research Network, 2013[67]	South East Asia	≥1	Inpatient	13	326	260	04/2007–02/2010	Oseltamivir	No virological or clinical advantages with double dose of Oseltamivir
Liu Y 2014[68]	China	18–65	Inpatient/ Outpatient	5	48	34	01/2011–03/2011	Clearing Heat and Detoxifying Injection (CHDI) or Oseltamivir	CHDI have a similar effect to Oseltamivir in reducing the duration of influenza illness
deJong MD 2014[69]	21 countries	≥6	Inpatient	323	398	338	09/2009–11/2012	Peramivir or placebo	No significant benefit for Peramivir plus SOC compared with placebo plus SOC
Higashi F 2014[70]	Japan	>15	Outpatient	1	79	49	12/2010–03/2011, 12/2012–03/2013	Oseltamivir, Zanamivir, Peramivir, Clarithromycin	Clarithromycin may have the additional clinical benefit of improving fever, in patients treated with neuraminidase inhibitors
Ison MG 2014[71]	USA, Canada, Mexico, Australia	≥6	Inpatient	59	234	127	10/2009–10/2010	Peramivir	IV Peramivir in hospitalized subjects demonstrates that 1× or 2× daily administration is associated with decrease in viral shedding and clinical improvement
Kakeya H 2014[72]	Japan	20–91	Undisclosed	14	107	107	12/2010–03/2011	Azithromycin, Oseltamivir	No significant difference in inflammatory cytokine expression level. Combination therapy showed an early resolution of some symptoms
Raus K 2015[73]	Czech Republic	≥18	Outpatient	29	473	473	11/2011–04/2013	Oseltamivir + placebo, *Echinacea Purpurea*	*Echinacea Purpurea* is as effective as Oseltamivir in early treatment of influenza
Dixit R 2015** [16]	Australia	≥5	Inpatient/- Outpatient	2	52	52	04/2011–08/2011	Oseltamivir	DD Oseltamivir did not appear to provide a clinical or virological advantage, but small sample size
Nakano T 2016[74]	Japan	≤10	Outpatient	50	343	343	11/2014–03/2015	Laninamivir octanoate or placebo	A single dose of Laninamivir octanoate was effective and well tolerated as prophylaxis for influenza
Dawood FS 2016**[75]	El Salvador, Panama	0–9	Inpatient	5	405	30	09/2012–10/2012, 04/2013–10/2013	Oseltamivir or placebo	Oseltamivir treatment was well tolerated amongst hospitalized children, including amongst infants aged <1 year
Jefferies S 2016[76]	New Zealand	18–65	Inpatient	1	80	46	07/2011–09/2012	Paracetamol or placebo	Regular paracetamol had no effect on viral shedding, temperature or clinical symptoms
Nakamura S 2017[77]	Japan	≥18	Inpatient/ Outpatient	16	92	92	12/2012–05/2014	Peramivir or Oseltamivir	Peramivir is a useful option for treatment of influenza-infected patients with high risk factors.
Vanchiere J 2017*[78]	USA	0–17	Undisclosed	Multi	108	N/A	Undisclosed		Treatment with Peramivir and Oseltamivir are well tolerated and safe.
Marty FM 2017[79]	International	≥16	Inpatient	97	626	488	01/15/2011 02/12/2015	Zanamivir or Oseltamivir	Time to clinical response to intravenous Zanamivir dosed at 600 mg was not superior to Oseltamivir or 300 mg intravenous Zanamivir
Liu Y 2017[80]	China	18–65	Outpatient	9	236	223	01/2014–03/2014	*Re*-Du-Ning or Oseltamivir	RDNI was well tolerated with no significant difference compared to Oseltamivir
Lee N 2017[81]	Hong-Kong	≥18	Inpatient	2	50	50	2013–2014 through 2015–2016	Oseltamivir and azythromycin	Found significant anti-inflammatory effects with adjunctive macrolide treatment in adults with severe influenza infection
Popov AF 2018[82]	Russia	21–60	Inpatient	1	200	200	12/2013–03/2016	Umifenovir (UMI) UMI + oseltamivir, UMI + Kagocel, Oseltamivir + Kagocel	Study demonstrated that combination of Oseltamivir and Umifenovir with Kagocel significantly increases therapeutic efficacy compared with monotherapy.
Ramirez J 2018[83]	USA	≥18	Inpatient	9	1107	96	2010–2013	SOC, SOC + Oseltamivir	Initiation of Oseltamivir >5 days after illness onset did not reduce clinical failures amongst hospitalized patients.
Hirotsu N 2018[84]	Japan	4–12	Outpatient	1	123	123	01/2014–03/2015	Oseltamivir, Zanamivir, Peramivir, Laninamivir	Time to virus clearance was significantly shorter with Peramivir vs Oseltamivir

References in supplement

* Numbers of confirmed influenza patients not provided by study.

** Study using ED as primary recruiting site.

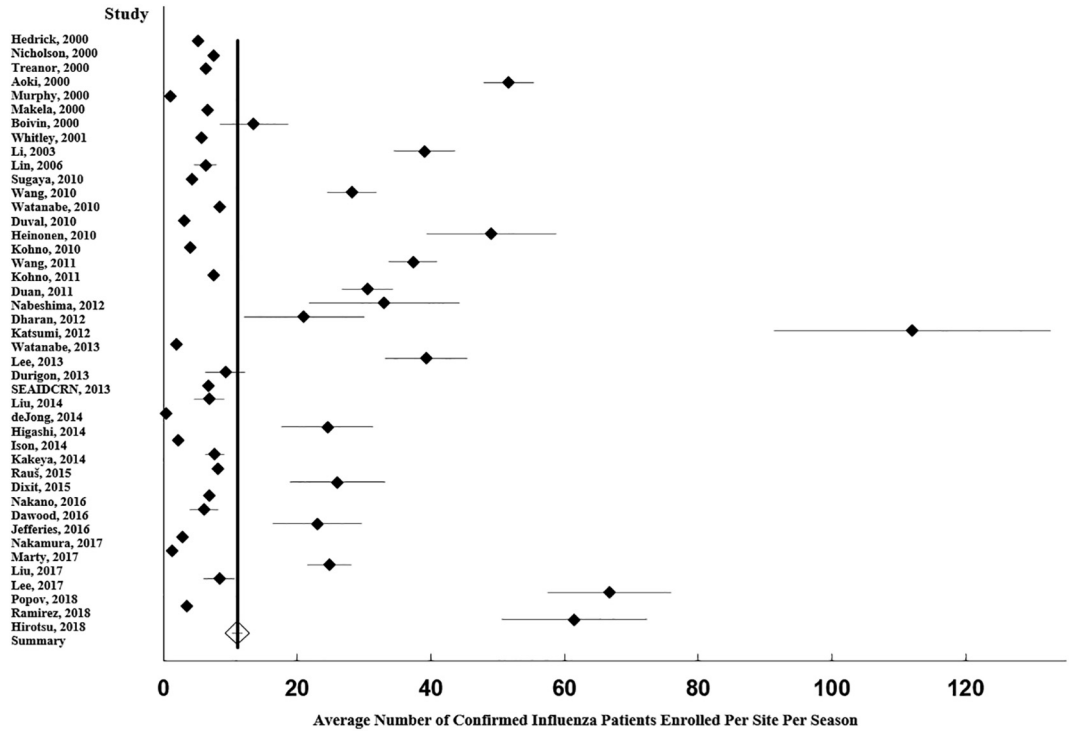

Fig. 2. Average number of confirmed influenza positive patients enrolled per study, per site, per season.
Blank diamond shape and the dark vertical line indicate the point estimate [11.0, (95%CI: 10.2, 11.8)] and the x-axis value of the pooled average number of confirmed influenza-positive participants enrolled per site per season. Solid diamond shape and the flanking horizontal lines indicate the average number of confirmed influenza-positive participants enrolled per site per season and its corresponding 95% confidence interval of each study included.

6. Conclusion

Randomized phase III clinical trials of influenza therapeutic trials have principally enrolled patients in inpatient or outpatient (non-ED) clinical settings and enrolled 11 participants on average, a relatively low number of subject enrollment per site per season. Most have relied on using many sites to achieve targeted sample sizes. Based on our recently published ED demonstration study, in which we enrolled 60 patients per site per season, as well as the known high rates of ED visits for respiratory illness during pandemics (including the COVID-19 pandemic), untapped likely opportunities exist for EDs to lead and/or participate more broadly in therapeutic RCTs for influenza and other emerging respiratory pathogens.

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Author contributions

Y-HH, and RER conceptualized the study. Y-HH, MY, NP, AH, M-CA, KL, and RER developed the study methodology. MY, NP, AH, and M-CA did the initial curation of data. MY and NP did the final curation of data. Y-HH, MY, and JDN conducted the formal analysis. Y-HH, MY, JDN, RER, and KS-S validated the results. JDN, MY, RER, and Y-HH drafted the manuscript. All authors critically reviewed all drafts of the manuscript.. All authors have seen and approved the final version of this manuscript.

CRediT authorship contribution statement

Richard E. Rothman: Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Joshua D. Niforatos:** Writing – review & editing, Writing – original draft, Validation, Supervision, Formal analysis, Data curation. **Mehdi Youbi:** Writing – review & editing, Writing – original draft, Validation, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Nicholas Polydefkis:** Writing – original draft, Investigation, Data curation, Conceptualization. **Alaina Hergenroeder:** Writing – review & editing, Visualization, Validation, Software, Methodology, Investigation, Formal analysis, Data curation. **Michele-Corinne Ako:** Writing – original draft, Visualization, Validation, Software, Resources, Formal analysis, Data curation, Conceptualization. **Katie Lobner:** Writing – review & editing, Supervision, Software, Resources, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Kathryn Shaw-Saliba:** Writing – review & editing, Visualization, Software, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Yu-Hsiang Hsieh:** Writing – review & editing, Writing – original draft, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of Competing Interest

The authors have declared that no competing interests exist.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajem.2022.09.003.

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