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Design and methods of a social network isolation study for reducing respiratory infection transmission: The eX-FLU cluster randomized trial

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ABSTRACT

Background: Social networks are increasingly recognized as important points of intervention, yet relatively few intervention studies of respiratory infection transmission have utilized a network design. Here we describe the design, methods, and social network structure of a randomized intervention for isolating respiratory infection cases in a university setting over a 10-week period.

Methodology/principal findings: 590 students in six residence halls enrolled in the eX-FLU study during a chain-referral recruitment process from September 2012–January 2013. Of these, 262 joined as “seed” participants, who nominated their social contacts to join the study, of which 328 “nominees” enrolled. Participants were cluster-randomized by 117 residence halls. Participants were asked to respond to weekly surveys on health behaviors, social interactions, and influenza-like illness (ILI) symptoms. Participants were randomized to either a 3-Day dorm room isolation intervention or a control group (no isolation) upon illness onset. ILI cases reported on their isolation behavior during illness and provided throat and nasal swab specimens at onset, day-three, and day-six of illness. A subsample of individuals ($N = 103$) participated in a sub-study using a novel smartphone application, iEpi, which collected sensor and contextually-dependent survey data on social interactions. Within the social network, participants were significantly positively assortative by intervention group, enrollment type, residence hall, iEpi participation, age, gender, race, and alcohol use (all $P < 0.002$).

Conclusions/significance: We identified a feasible study design for testing the impact of isolation from social networks in a university setting. These data provide an unparalleled opportunity to address questions about isolation and infection transmission, as well as insights into social networks and behaviors among college-aged students. Several important lessons were learned over the course of this project, including feasible isolation durations, the need for extensive organizational efforts, as well as the need for specialized programmers and server space for managing survey and smartphone data.

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1. Introduction

Isolation, defined as separating sick individuals from healthy ones, is an integral public health measure for preventing transmission of infectious diseases (Ferguson et al., 2006; Aledort et al., 2007; Bell et al., 2006). Contact mixing patterns have been shown to be important in the spread of airborne pathogens (Edmunds et al., 2006, 1997; Melegaro et al., 2011; Wallinga et al., 1999;

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Mossong et al., 2008; Eames et al., 2010; Van Kerckhove et al., 2013). Few studies, however, have examined the effect of isolation on the spread of influenza to the social contacts of ill individuals (Aledort et al., 2007; Jefferson et al., 2011). One reason for the lack of research examining the impact of these measures, in particular, on influenza transmission is the difficulty in assessing whether individuals who are in contact with an index case are, in fact, protected by that individual's isolation (Ball and Neal, in press; Germann et al., 2006). Indeed, such a study requires enumeration of a social network prior to any cases arising within the network and longitudinal collection of detailed information about the timing, duration, intensity, and setting of contacts between index cases and any members of their social network, after an individual's illness onset (Edmunds et al., 2006; Melegaro et al., 2011; Mossong et al., 2008; Lee et al., 2008). Furthermore, to test whether these measures reduce transmission of infectious disease within a social network, index cases must be randomized to engage in isolation as soon as they become ill. While the importance of social networks in the transmission of influenza has been increasingly recognized (Mossong et al., 2008; Cauchemez et al., 2011; Glass et al., 2006; Glass and Glass, 2008), experimental studies examining the effect of isolation or quarantine on transmission remain limited (Aledort et al., 2007; Jefferson et al., 2011).

Here we describe the study population characteristics and social network structure of 590 students living in residence halls of a large public university who were recruited via a chain referral process and randomized to an intervention of isolation over a 10-week period during the 2013 influenza season. While chain referral (i.e., snowball sampling) and other similar approaches have been used successfully in a variety of infection transmission studies (Ding et al., 2005; Ghani and Garnett, 2000; Harris et al., 2006; Kendall et al., 2008; Gyarmathy et al., 2014), we additionally overlaid a randomized intervention onto a chain referral sample and employed multiple dynamic approaches for collecting data on social interactions among enrolled participants prospectively over time. Data collected in this study will be subsequently used to test the impact of isolation on transmission of influenza-like illness (ILI) – defined as cough plus fever/feverishness, or body aches, or chills – as well as laboratory-confirmed influenza and other respiratory infections among the social network of cases in our study. While the intervention tested in this study was isolation, the methods used (i.e., a chain referral sampling and prospective collection of objective and self-reported data on face-to-face social interactions between enrolled individuals) are applicable for a wide range of potential studies aimed at exploring the relationship between social interactions, isolation, quarantine, and disease transmission. In addition, we describe a sub-study within the social network of study participants in which iEpi, a smartphone application, was used to collect objective sensor and contextually-dependent survey data on extensive social interactions between individuals enrolled in the study.

2. Methods

2.1. Trial registration

This study was registered at Clinicaltrials.gov, study # NCT01472536. The CONSORT checklist is available in Fig. 1.

2.2. Ethics statement

The study was approved by the Institutional Review Board (IRB) at the university where the study was carried out, HUM00054432. The CDC's Human Subjects Research Office reviewed and approved deferral to said university's IRB. Informed consent was obtained from all participants through electronic signature of an online consent form. Written consent was obtained from participants prior to specimen collection for diagnostic testing.

2.3. Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of CDC.

2.4. Setting and study design

Six of the university's twelve residence halls were included in this study. These residence halls were identified by University Housing as representative of the larger student population at the university—encompassing both specialized dormitories in which resident students share specific fields of study and more general dormitories housing diverse student populations. The largest residence hall housed 1259 residents and the smaller halls ranged in size from 401 to 1184 residents. Prior to the start of participant recruitment, each of the six residence halls were sub-divided into 117 similarly sized clusters based on factors likely to influence social interactions between residents, including residence house assignment, resident advisor jurisdiction, geographic proximity of residence hall rooms, and physical building barriers (e.g., location of shared bathrooms, staircases, doors, and/or firewall dividers), as illustrated in Fig. 2. There were an average of 48 (range 24–90) eligible students per cluster.

Clusters were randomized to the 3-Day intervention or control groups using a randomized block design with residence hall as the blocking factor so all clusters within a residence hall had an equal likelihood of being selected for any of the study arms. Study staff used PROC SURVEYSELECT and PROC PLAN in SAS 9.2 (Cary, NC, USA) to generate and implement the random allocation sequence, resulting in a well-balanced cluster distribution of the two study groups within each residence hall. Study staff involved in the generation and implementation of the randomization process, were not involved in the recruitment of participants.

2.5. Recruitment methods and eligibility

Students ≥18 years of age and living in one of six selected residence halls were eligible for study participation. Undergraduate residence halls are sub-divided into houses – within which residents share residence advisors, bathrooms, and small common areas – and houses are further divided into single rooms, double rooms, or suites that house three or four students. To determine eligibility, the names of all individuals living in each of the six eligible residence halls, along with their house and room number, were included in a list provided by University Housing to study staff before participant recruitment began in September 2012. Study staff recruited individuals at informational tables and through a study website. Informational flyers about the study were also posted across campus. Students who signed-up to receive more information about the study (in-person, through the study website, or by phone or email) received an enrollment invitation email. Each enrollment invitation email contained a unique link to a web-based enrollment system that verified participant eligibility and provided an online consent form for participation. An electronic signature confirmed consent. Enrolled participants were asked to complete the enrollment survey and nominate social contacts living in one of the six eligible residence halls to join the study. As part of the web-based enrollment system, participants could search by name or university email address for individuals whom they wished to nominate to join the study. Nominated social contacts were verified as eligible by cross-checking the name and/or university email address provided against the list of eligible individuals provided

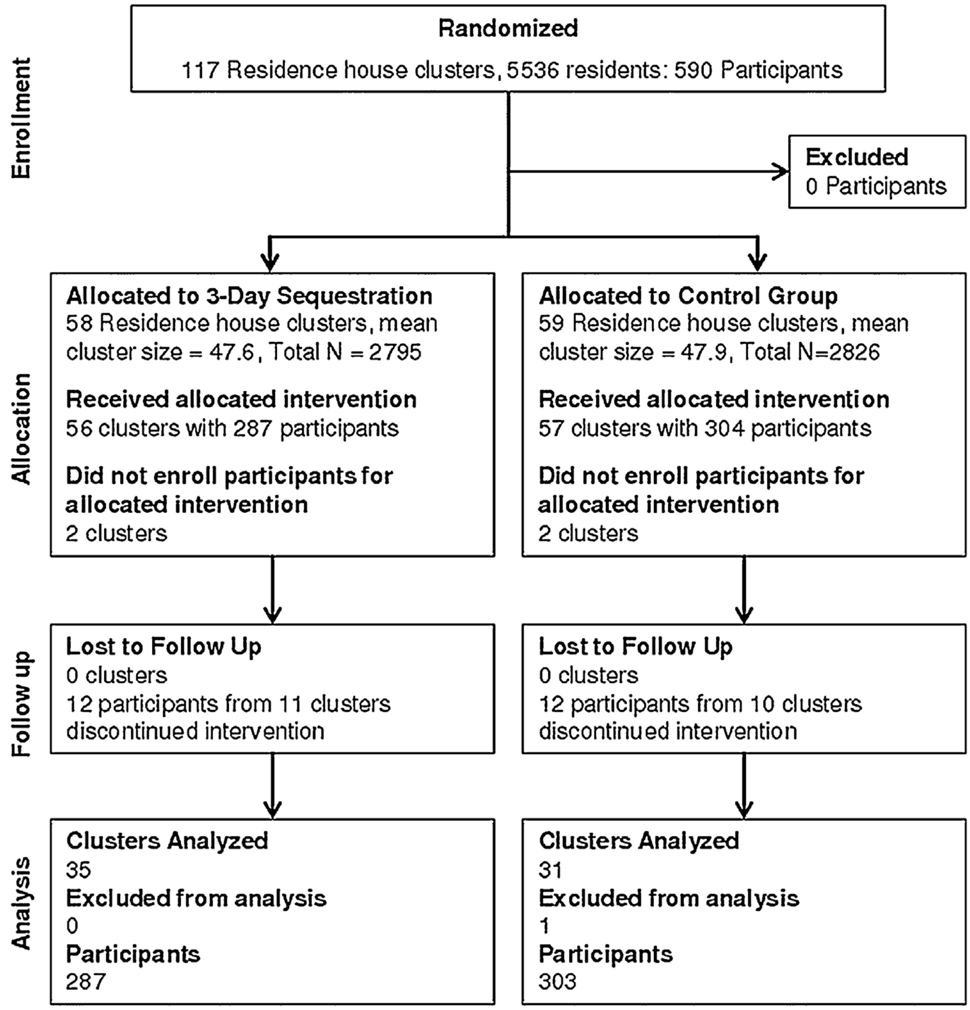

Fig. 1. eX-FLU Consort diagram.

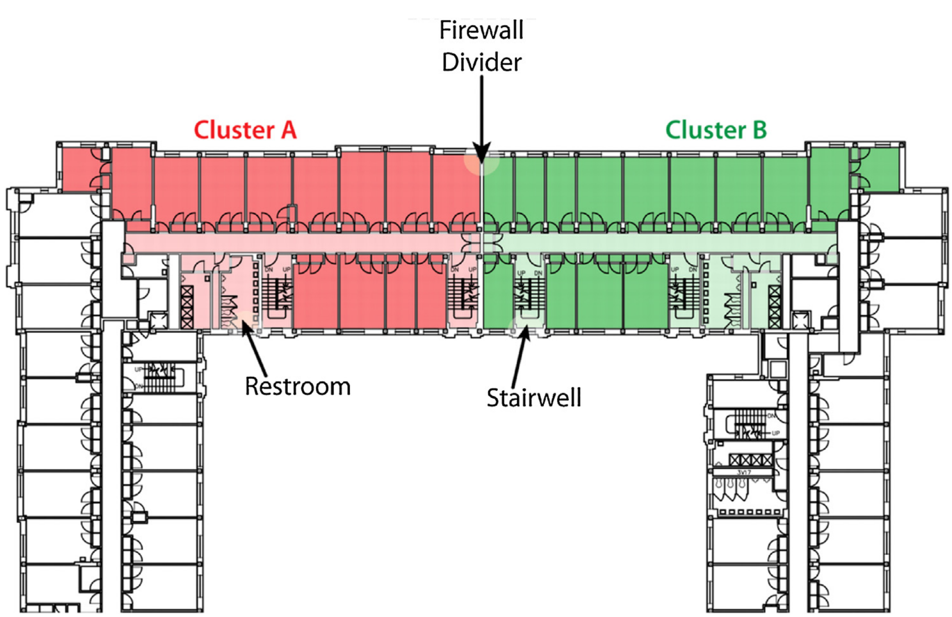

Fig. 2. *Cluster example.* An example showing how clusters are determined within a residence hall, based on a range of factors, including resident advisor jurisdiction, geographic proximity of residence hall rooms, and physical building barriers such as location of shared bathrooms, staircases, doors, and/or firewall dividers.

by University Housing, and all nominated social contacts determined to be eligible for study participation subsequently received an enrollment invitation email from the nominating participant's university email address. University-issued email addresses were used to communicate with participants throughout the study.

Chain referral sampling was employed whereby nominated social contacts were then asked to complete the same enrollment and social contact nomination process, generating multiple waves of nominations throughout the enrollment period. Participants who enrolled in the study through an enrollment invitation email sent directly from study staff were considered '*seeds*,' and participants who enrolled by accepting the nomination of an enrolled participant were considered '*nominees*.' Individuals who did not enroll in the study were not assigned an enrollment type. Each participant received $10 following successful enrollment and $15 for the successful enrollment of up to three of their nominated social contacts (a maximum of $45). For each enrolled participant, an additional $5 was given to the first three of their nominees who accepted their invitation to join the study. Individuals who started the enrollment process or were nominated to join the study received up to three emails reminding them to complete the enrollment process and participants were emailed updates regarding the enrollment status of their nominations. In January, all fully enrolled participants were entered into a raffle for an Amazon Kindle, as a further incentive to complete the enrollment process.

2.6. Baseline survey

All surveys were web-based (Qualtrics, Provo, UT) and administered through email to study participants. The baseline survey was administered at the start of the intervention period and collected data on health behaviors, pandemic preparedness knowledge, psychosocial characteristics, influenza transmission knowledge, and measures of perceived social support (see Appendix SA1 for more details and definitions of baseline measures).

2.7. Weekly surveys

Each Friday during the 10-week intervention period, participants were administered a survey via email that expired the following Tuesday at midnight. On each weekly survey, participants were prompted to report if they had face-to-face contact with other participants over the past seven-day period. Contacts who had been previously reported on a weekly survey were pre-populated in the online survey and, for new face-to-face contacts, participants could search for individuals by name or university email address and report contact if the individual was confirmed as a study participant. For all reported face-to-face contacts, participants were asked whether these individuals exhibited the following symptoms of respiratory illness: cough, sneezing, runny nose, fever or feverishness, chills, or body aches. In addition, participants were asked to report whether they had a roommate who exhibited any of these symptoms over the past seven-day period, irrespective of whether their roommate(s) were themselves study participants. Additional information was collected about social interactions with the three study participants with whom participants reported having the most face-to-face contact, including date, duration (in minutes), contact's relationship to the participant (classmate, study partner, teammate, romantic, family member, co-worker, roommate, or other relationship), and contact setting (residence hall room or common room, cafeteria, computer room, library, restaurant, pub/bar, coffee shop, party or social event, fitness center, friend's house, public transportation, intramural or club sports, workplace, or other outdoor location or activity). Participants were also asked to report their hand hygiene habits, average number of hours spent in their residence hall room, and overall health. Lastly, participants were asked to report any symptoms of illness to study staff (e.g., cough, abdominal pain, sore throat, fever or feverishness) in the weekly survey and to specify the severity of each of their symptoms as well as the date and time of symptom onset. The final weekly survey additionally asked students to report their class schedules for the Winter 2013 semester (department, course title and number, meeting day/time, professor), which were verified and matched with courses listed in the University's official course schedule, provided by the Registrar, during the data cleaning phase of the study. Participants who had not completed their weekly survey within three days of receipt were sent an email reminder.

2.8. Intervention

The intervention period began after confirmation of laboratory-diagnosed influenza transmission on the university campus on January 17, 2013, and continued for 10 weeks until April 9, 2013, excluding a one-week long university-wide winter recess in mid-February, during which the majority of students were not on campus.

2.9. ILI protocols

At the beginning of the 10-week intervention period, all participants received an illness kit with study protocol instructions, a thermometer, facemasks (3-Day isolation group only), and information for preventing influenza transmission. All participants were asked to report the following symptoms to study staff: cough, sneezing, runny nose, fever or feverishness, chills, or body aches. Participants reported symptoms via the weekly survey or by phone, email, or a web-based symptom reporting system. We defined ILI as a cough plus at least one of the following symptoms: fever or feverishness, chills, or body aches. This broad ILI definition, previously used in another recent influenza study in a college population (Aiello et al., 2010, 2012), was used in order to capture influenza cases both with and without fever (Thursky et al., 2003). Participants meeting the case definition for ILI were surveyed about feelings of anxiety and were immediately offered time slots for scheduling a specimen collection appointment via the web-based survey system. Additionally, upon meeting the case definition for ILI, individuals who were randomized to the 3-Day isolation intervention group were instructed to immediately begin their isolation protocol and remain in their residence hall room for three days (i.e., 72 h from symptom onset). Control group participants were not asked to engage in isolation beyond their normal or preferred illness behavior and were given basic information about influenza transmission control methods (i.e., washing hands frequently and using a tissue to cover the nose and mouth while sneezing). In order to encourage adherence to the 3-Day isolation protocol, study staff were available to deliver to intervention group participants packages containing snacks, beverages, and sufficient provisions for the three-day isolation period. If requested, study staff assisted individuals participating in isolation with communications to faculty and employers about his or her illness and/or participation in the study including a doctor's note verifying illness and documenting participation in the study. Web-based surveys were sent to all ILI cases in both study groups 72 h after their reported symptom onset date and time. These ILI-related surveys collected data on the number of hours participants spent in their residence hall room, reasons participants left their residence hall room (e.g., to go to class or receive medical attention), and feelings of loneliness and anxiety experienced on the day of symptom onset and during the three subsequent days. At the end of the study period, regardless of whether they were an ILI case during the 10-week intervention period, students randomized to the 3-Day isolation group received an additional $50 for participation and students randomized to the control group received an additional $30 for participation in the study.

2.10. Specimen collection

Participants who reported symptoms meeting the ILI case definition were immediately invited to use the study's online scheduling system to arrange their first specimen collection appointment. Throat and nasal swab specimens were collected within 24 h of illness onset (for ILI cases who reported symptoms within 24 h of symptom onset), and subsequently at three and six days after illness onset. Collection of specimens from each participant at three time points after illness onset was performed in order to assess viral shedding patterns over the illness period. Study staff visited participants in their residence hall rooms to obtain written consent and to collect a total of five specimens (three nasal swab specimens and two throat swab specimens). During the specimen collection appointments, study staff also collected information about the participant's temperature, recent use of antipyretics, and current illness symptoms. Participants were offered $10 for participating in a single specimen collection appointment, $15 for participating in a second appointment, and $20 for participating in a third appointment.

Specimens were also collected from healthy contacts of ILI cases. When a participant reported symptoms meeting the study criteria for ILI, other participants with whom the ILI case reported having social contact on the most recent weekly survey were invited to provide "healthy contact" specimens. We aimed to collect samples from at least two healthy contacts per ILI case to assess either early stage infection or asymptomatic carriage of viruses or bacteria. Specimens were collected following the same protocol used for ILI cases, and healthy contacts received the same compensation for providing specimens as ILI cases.

2.11. Laboratory protocol

A total of five swabs were collected from participants at each specimen collection appointment (i.e., within 24 h of illness onset, three days after illness onset, and six days after illness onset): one double-headed swab from a single naris, stored in viral transport media (VTM) and LDM50; a second double-headed swab from the throat, stored in VTM and skim milk media; and a single-headed swab taken from the second nares and stored in VTM for rapid influenza testing. Using quantitative PCR, the laboratory protocol included testing for the presence of influenza A and B, as well as other non-influenza respiratory viruses (human metapneumovirus [hMPV]; rhinovirus; parainfluenza 1, 2, and 3; adenovirus; respiratory syncytial virus [RSV]; and coronaviruses 229E, OC43, NL63, and HKU). Remaining aliquots were stored separately for future testing of samples. Methods for testing and storing of specimens followed previously established protocols (Aiello et al., 2010, 2012).

2.12. iEpi smartphone application sub-study

During the intervention period, a subsample of participants ($N = 103$) were provided a Samsung Galaxy™ NEXUS™ i9250 smartphone equipped with *iEpi*, an existing smartphone application that collects sensor and contextually-dependent survey data used to geo-locate participants on campus and record and encrypt data relevant to social interactions between iEpi sub-study participants during the course of the intervention period (Hashemian et al., 2012; Knowles et al., 2014). While several other researchers have employed various technologies to perform automated contact tracing for examining disease spread (Eagle et al., 2009; Madan et al., 2010; Smieszek et al., 2014; Salathe et al., 2012; Stehlé et al., 2011), to the best of our knowledge, this is the first time this technology has been employed with an intervention specifically targeting the dynamic structure of the contact network. In order to maximize the likelihood of collecting data on the social interactions between participants who enrolled in the iEpi sub-study, we prioritized recruitment of participants into the sub-study who were most likely to interact with one another during the course of the intervention period. These participants were identified by constructing a network graph using information on nominations from our chain referral sample. We divided the resulting network into communities based on modularity (Newman, 2006) by using a recursive edge-deletion algorithm to determine community partitions (Girvan and Newman, 2002). Starting with the largest community, we randomly selected participants to receive an email invitation to participate in the iEpi sub-study. We continued to recruit participants within the communities, starting with the largest community, until we successfully enrolled the total number of participants in our pre-determined subsample population ($N = 103$). Students accepting the invitation to participate in the iEpi pilot study provided written informed consent and attended an iEpi training session.

The iEpi sub-study participants were asked to carry the study phones with them 24 h a day, charge their phone every night, report any technical issues to research staff, and keep their study phone in "discoverable mode" to enable the iEpi application to detect Bluetooth® and WiFi® devices on the university campus. When encountering a remote device in discoverable mode, the iEpi application on an index device recorded a range of variables, including the media access control (MAC) address, which provides a unique identifier for the device, the device type, a timestamp for device contact, the received signal strength indicator (RSSI), and the WiFi hotspot router, to allow for geo-locating study participants on campus. Bluetooth detection of one smartphone by another was used to estimate the likelihood that any two iEpi sub-study participant smartphones were within a few meters of each other during the course of the intervention period (Bluetooth detection typically operates on distances up to 5–10 m). Additionally, Bluetooth detection of other devices enabled in "discoverable mode" – including phones, tablets, and computers outside of the study – allowed us to estimate the overall level of social contact of iEpi sub-study participants with individuals outside the iEpi sub-study. The iEpi application also collected 3-axis accelerometer data to assess mobility, charging state, battery level (to identify loss of data due to battery failure), and battery temperature (to monitor fluctuations in temperature when transitioning between indoor and outdoor environments). Data were collected at five-minute intervals from January 28, 2013 to April 15, 2013.

If one or more iEpi sub-study smartphones detected each other via Bluetooth, the iEpi application also randomly triggered a brief contextually-dependent survey to be sent to each participant's phone. The surveys asked questions regarding the participants' face-to-face interactions with other iEpi sub-study participants whose smartphones were detected via Bluetooth, such as whether they were in the same room and/or touching each other (see Supplementary Fig. S1 for a screenshot of the iEpi survey). Participants received surveys only between 9:00 AM and 10:00 PM. If a participant did not respond to a survey within ninety minutes, the survey timed out and disappeared from the phone. Participants could opt out of sensor and survey data collection at any time by selecting the "SNOOZE" function on the iEpi application, which blocked data collection for up to twelve hours in half-hour increments. While no sensor data were recorded during this time, data was recorded in a way that differentiated between the initiation of the "SNOOZE" function and a turned-off or malfunctioning phone. This helped us identify and correct any potential hardware or software problems with the phones or iEpi application.

Participants completing the iEpi sub-study were able to keep the phone at the completion of the study (average purchase value as of January 2013: $389). Individuals who un-enrolled from the iEpi sub-study during the intervention period were asked to return the smartphones to study staff. The iEpi sub-study participants received an additional $20 at the conclusion of the study if they responded to at least 75% of the contextually-dependent surveys triggered on their phone.

2.13. Pilot study year

During a mild influenza season in 2012, we conducted an 8-week pilot study to determine the tolerable duration of isolation (three or six days) for the intervention, as well as to test the feasibility of the overall study design. The pilot study was identical to the main study design described here, except we also randomized students to a 6-Day intervention group in which students were asked to stay isolated in their room for six days from the onset of illness. Of the 584 individuals who enrolled in the pilot study, 10 withdrew prior to the start of the intervention, resulting in 574 total participants. On the pilot study's exit survey, only 7.0% of respondents reported they would be willing to participate in isolation for four or more days in a future study. In addition, the highest level of adherence to isolation during illness was among those in the 3-Day isolation group (for the first four days post-ILI onset, cases from the 3-Day group spent an average of 72% of each day in their room, compared to 57% for the six-day group). These data were utilized to develop the main study design, which implemented a 3-Day isolation group versus a control group during the 2013 influenza season. Additionally, small changes to data collection (e.g., survey skip patterns and how individual data was linked across various surveys) were made in response to challenges study staff encountered while cleaning pilot year data.

3. Analysis and assessment

3.1. Participant characteristics

The means and frequencies of demographics, health behavior, health status, and psychosocial characteristics were estimated for the entire study population, as well as by enrollment type (seed versus nominee), intervention group, and iEpi sub-study participation group. For continuous variables with non-normal distributions, the median and interquartile range (IQR) were also calculated. Statistical significance of differences by enrollment type and iEpi participation were calculated using Pearson's Chi-squared and Wilcoxon Rank-Sum tests; *P*-values less than the Bonferroni corrected alphas of 0.05 were considered significant. Variable derivation and categorization are available in Appendix SA1. Statistical analyses were performed in R (Vienna, Austria) and SAS 9.3 (Cary, NC, USA).

3.2. Study participation

The mean and median number of nominations (i.e., indegree) nominees who enrolled in the study received from either seeds or nominees who had already enrolled in the study was compared to nominations received by individuals who were nominated but did not subsequently enroll was analyzed via Wilcoxon Rank-Sum test. The frequencies, means, and medians for numbers of weekly surveys completed and numbers of contacts reported on weekly surveys by participants, overall, and by intervention group were calculated. In order to determine if the additional participation requirements for ILI cases (both overall and for the intervention group) resulted in lower engagement overall, we assessed weekly survey participation in each of the different groups. The mean number of weekly surveys completed by participants who were ILI cases at least once during the study period was compared to the mean number completed by non-ILI cases using a linear mixed model. Additionally, differences in number of weekly surveys completed between ILI cases in the control group and those in the 3-Day group were compared; these numbers were also calculated via linear mixed model.

3.3. Nomination and study period social networks

An overview of basic social network terminology, formulas, and definitions used in the following analyses are given in Appendix SA2 and a summary of the study's social networks are shown in Table 1. Social networks for the enrollment chain referral process ("Nomination Network") and all face-to-face contacts reported on the weekly surveys were constructed (the "Week (1–10) Network" networks and "Combined Weekly Network"). The Nomination Network consists of individuals who were nominated to join the study (both those who subsequently enrolled and those who did not join the study) as well as eligible students who requested an enrollment email directly from study staff but did not subsequently enroll. For the contacts reported on the weekly surveys, a separate directed network for each week was generated ("Week (1–10*)* Networks") and these ten networks were then condensed into a single, undirected network containing all participants and contacts between

Table 1
A summary of eX-FLU's social networks.

	Nomination Network	Week X (1–10) Network	Combined Weekly Network
Nodes	All eligible students who requested an enrollment email from study staff or were nominated by a participant	All enrolled participants	All enrolled participants
Edges	A nomination from a participant to an eligible student or roommates	A face-to-face contact between two participants reported on week X's survey	A face-to-face contact between two participants reported at least once during the study period
Edge type(s)	Directed (nominations) and undirected (roommates)	Directed	Undirected
Total degree	Total number of other participants linked to a given participant by a received or sent nomination and/or roommates	Total number of participants with whom a given participant had contact with during week *X*	Total number of participants with whom a given participant had contact with during the full intervention period
Indegree	Number of nominations received	Total number of participants who reported contact with a given participant with during week X	N/A
Outdegree	Number of nominations sent	Total number of participants with whom a given participant reported contact with during week X	N/A

them over the entire intervention period ("Combined Weekly Network").

The edges in the sub-graph of the Nomination Network containing only enrolled participants and nomination links were compared to the edges in the Combined Weekly Network in order to identify overlap, i.e., how much of the potential-transmission network during the study period was captured by the Nomination Network, and conversely what edges may have appeared in the Combined Weekly Network but not in the Nomination Network. We also evaluated what fraction of reported contacts (directional edges) were reciprocal in each of the 10 Week networks.

In order to characterize the enrollment process, study participation, and any relationships between them, we evaluated social network characteristics for the Nomination Network, as well as a subset of characteristics for the individual Weeks and Combined Weekly Networks, and compared some measures across the multiple networks. Network analyses that required personal, self-reported information for individuals (e.g., assortativity) were conducted using only enrolled participants who had provided relevant data on the enrollment and baseline surveys. We used the package NetworkX in Python 2.7 for all social network analyses (Oliphant, 2007) and visualized the social network graphs in Visone 2.7 (Konstanz, Germany).

Indegree, outdegree, and total degree were quantified for the networks, as described in Table 1. We note that in the Nomination Network, outdegree for all nominated individuals that did not enroll in the study was zero, as only enrolled participants could nominate other individuals to join the study. Similarly, eligible individuals who were not nominated to join the study by any participant, but requested an enrollment email from study staff, and chose not to enroll in the study had in- and out-degrees equal to zero. Means for total degree, indegree, and outdegree, as well as median and IQR, for enrolled individuals and for all individuals in the Nomination Network were calculated. Degree distributions were plotted for the Nomination Network and ten Week Networks and log–log linear trendlines were fitted using MS Excel (2010) for the Nomination and Combined Weekly Networks. Additionally, for the Nomination Network, differences in total degree, indegree, and outdegree between seeds and nominees were analyzed by Wilcoxon Rank-Sum test. We also calculated the network average clustering coefficient (Watts and Strogatz, 1998) and transitivity (i.e., proportion of all possible triangles present in the network (Girvan and Newman, 2002) for each network (Nomination and Week Networks).

Assortativity (i.e., the tendency of a participant to nominate or be linked to another individual with a shared characteristic (Girvan and Newman, 2002)) was calculated for a wide range of characteristics for the Nomination Network, using the largest number of individuals for whom the information on each characteristic was known. Assortativities by intervention group, residence hall, and residence house were calculated for all individuals in the Nomination Network. Assortativities by enrollment type (seed versus nominee), iEpi participation status, demographics, health behaviors, health status, and psychosocial characteristics were also estimated for enrolled individuals who provided information on the enrollment and/or baseline surveys. For assortativities by self-reported characteristics, any individuals who did not report information, either due to non-enrollment or non-response to that particular survey question, were dropped from the Nomination Network prior to assortativity calculation (as the assortativity calculations require the characteristic information for all network members). Thus, each assortativity was calculated for a reduced network containing only individuals who self-reported that characteristic. Additionally, when calculating assortativities, roommate links were removed from the network, as the purpose of assessing assortativity was to examine homophily within the chain referral process (i.e., whether individuals tended to nominate students with similar characteristics) as opposed to among roommates. To test for statistical significance of the assortativities, *P*-values, which can be interpreted as the probability of obtaining an assortativity as extreme as the observed assortativity under the null hypothesis of zero assortativity (i.e., no preferential connections between participants based on a given characteristic) were generated by bootstrapping using Python 2.7.

We also estimated closeness and betweenness centrality, two commonly used centrality measures for evaluating an individual's influence in a network (Anthonisse, 1971; Beauchamp, 1965; Freeman, 1977, 1978) for the Nomination Network. These measures are based on the shortest path distances (i.e., the path with the fewest edges) between an individual and the other members in the network. An individual's closeness centrality is the reciprocal of the mean of all such shortest paths and represents the average number of edges away that a given individual is from any other individual (Beauchamp, 1965; Freeman, 1978). Betweenness centrality is as the mean proportion of shortest paths including a given individual (Anthonisse, 1971; Freeman, 1977) and represents the number of shortest paths connecting two individuals in the network that pass *through* a given individual. Estimating closeness and betweenness centralities requires a connected network (i.e., so that a path exists between every pair of individuals in the network). Consequently, these measures were estimated for all individuals in the largest connected component of the Nomination Network. Additional information on these measures, and formulas for assortativity, closeness, and betweenness can be found in Appendix SA2.

3.4. iEpi sub-study bluetooth network assessment

We generated an additional social network graph for the iEpi sub-study, based on all recorded Bluetooth detections between phones of sub-study participants (i.e., each Bluetooth detection of a sub-study phone by another generated an edge/link within the network). This network was constructed and visualized with the NetworkX package in Python 2.7.

4. Results

4.1. Enrollment

During the study period, a total of 2229 individuals either signed up to receive an enrollment invitation email from study staff or were nominated by an enrolled participant, of which 590 (18.5%) individuals enrolled in the study. Among those who enrolled, 262 (44.4%) participants enrolled as seeds and 328 (55.6%) as nominees. Nominated students received, on average, 1.2 (standard error (SE: 0.05)) nominations and receiving a higher number of nominations was significantly associated with joining the study as a nominee (enrolled mean nominations: 1.7 (SE: 0.06), not enrolled mean nominations: 1.3 (SE: <0.01), $P < 0.0001$). The maximum number of nominations a nominee received was 7. The chain referral recruitment process resulted in 12 waves of nominations, as shown in Fig. 3. In this figure, an edge (i.e., the line connecting two individuals) represents the accepted nomination sent from a seed or nominee to a nominee in the next wave of chain referral. This network is directed, with each edge originating from the nominator and pointing towards a nominee who accepted their nomination. The Nomination Network shown in Fig. 4 highlights enrollment status (i.e., non-enrolled versus enrolled) and among enrolled participants, denotes whether individuals enrolled as seeds versus nominees. This network contains directed edges representing all nominations sent between all enrolled and nominated individuals and undirected edges between roommates. Of the 590 individuals

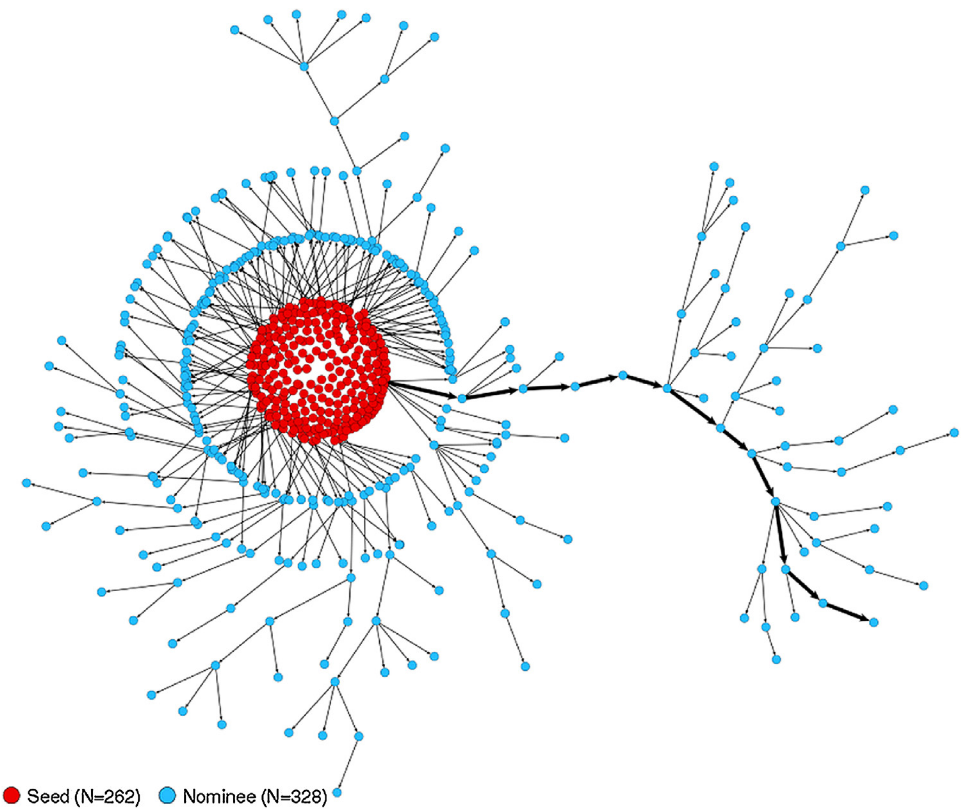

Fig. 3. *eX-FLU chain referral process (N = 590).* Each node (circle) in the network represents an enrolled eX-FLU participant. Nodes are colored according to enrollment status: seed (enrolled independently) or nominee (accepted an invitation, i.e., nomination, from a participant). Each accepted invitation from a participant is represented by an arrow, directed at the nominated individual. The highlighted arrows show an example of the longest chain in the chain-referral network, with a single seed initiating 11 subsequent waves of accepted nominations. The complete chain-referral process with these edges, as well as unaccepted nominations, is shown in Fig. 4. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

who enrolled in the study, 287 (48.6%) were randomized to the 3-Day intervention group and 303 (51.4%) to the control group. Eleven participants were re-assigned to the control group after moving out of an eligible hall between enrollment and the intervention period.

4.2. Demographics

Descriptive statistics of the demographic, health behavior, health status, and psychosocial characteristics of the study population are shown in Supplementary Tables S1–S3. The mean age of participants was 18.8 years ((SE): 0.04); 57.9% were female, and 67.4% were White (versus non-White). Characteristics of the study participants by enrollment type are also shown in Supplementary Tables S1–S3. There were no statistically significant differences in the demographics, health behavior, health status, and psychosocial measures between seeds and nominees. However, there was a small difference in age between seeds (mean 18.9 (SE: 0.05) and nominees (mean 18.6 (SE: 0.07)), $P = 0.02$).

Demographic, health behavior, health status, and psychosocial characteristics by intervention group are shown in Supplementary Tables S4–S6. There were few substantive differences in characteristics by intervention group, suggesting that the randomization procedure utilized in this study was successful.

We also compared study participant characteristics to that of the overall student population and the population residing in the University's on-campus residence halls. Importantly, our sampling showed very little bias as the majority of demographic characteristics (e.g., age, race, ethnicity, and citizenship) mirrored the residence hall population at the University for all undergraduate students in 2012, as well as students living on campus. The only difference was a slightly higher proportion of women (~60% in the study sample versus 50% for the general residence hall population). Thus, our study findings should be generalizable to the undergraduate population who live on-campus.

4.3. Study participation

Of the 590 individuals who enrolled in the study, 454 (78.9%) completed the baseline survey. Of those, 93.4% ($N = 424$) responded to at least one weekly survey and 83.5% ($N = 379$) responded to over half of the weekly surveys. Among individuals who responded to any weekly surveys, 52.6% ($N = 239$) responded to all 10. Across the 10 weekly surveys, participants reported an average of 3.6 (SE: 0.06) face-to-face contacts with other participants during the previous week, with a maximum mean of 3.8 (SE: 0.07) in week 5 and a minimum mean of 3.2 (SE: 0.2) in week 1. Among those who completed the baseline survey, participants who were ILI cases at least once during the study completed the same number of weekly surveys than non-ILI cases (ILI cases mean: 8.2 (SE: 0.3), non-ILI cases mean: 8.2 (SE: 0.1), $P = 0.88$). ILI cases in the 3-Day group completed slightly fewer weekly surveys than ILI cases in the control group, but this difference was not statistically significant (6.6 (SE: 0.46) versus 8.7 (SE: 0.31), respectively, $P = 0.06$).

4.4. Social network characteristics

Visualizations of the ten Week Networks and Combined Weekly Network are shown in Fig. 5. Overlap between the Nomination and Combined Weekly Network's edges are shown in Fig. 6. Eighty-five percent of nomination links between participants

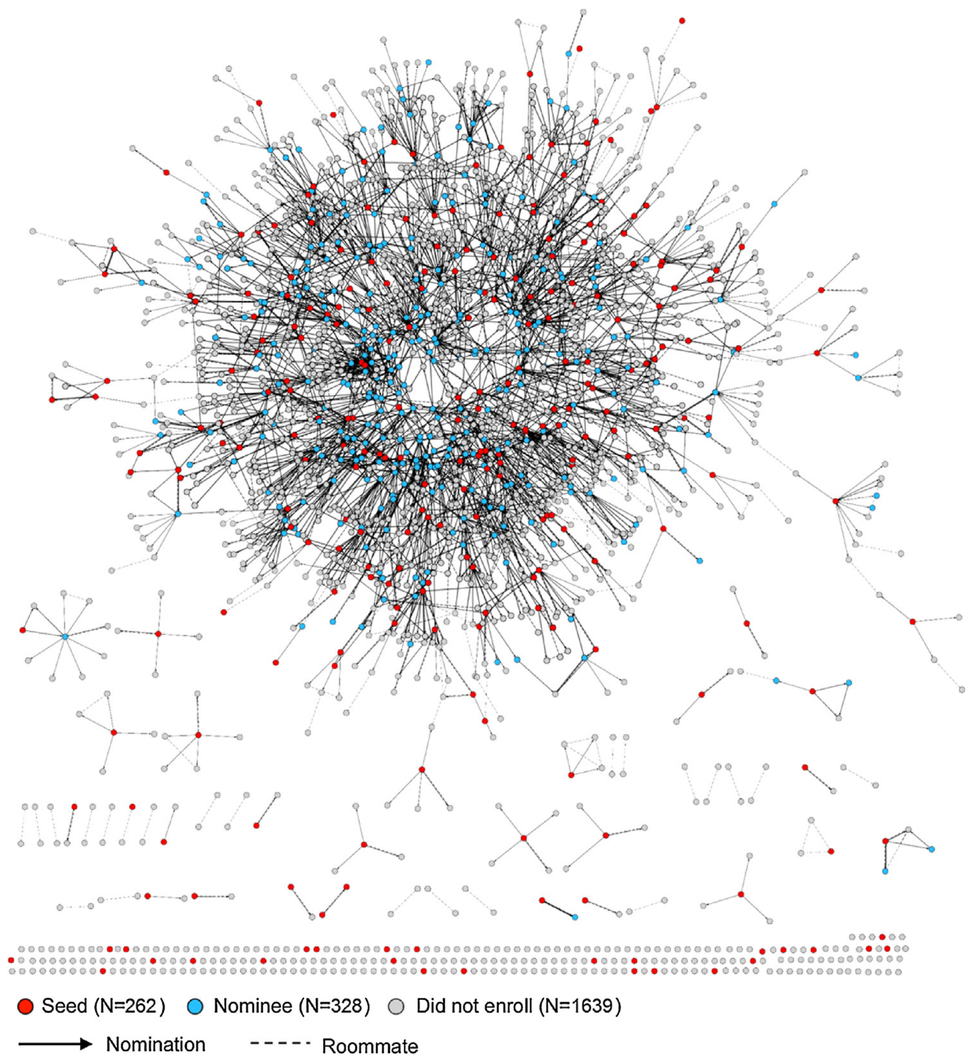

Fig. 4. *eX-FLU Nomination Network (N = 2229).* Each node (circle) in the network represents an eligible individual who received a nomination from an enrolled participant or an enrollment email from eX-FLU staff. Nodes are linked by a nomination edge (arrow), with the arrowhead directed at the nominee, and/or by a roommate edge (dashed line). Individuals who joined the study are colored according to seed (enrolled independently) or nominee (accepted an invitation, i.e., nomination, from a participant) status. Individuals who did not join the study are not colored. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

were also reported as face-to-face contacts on at least one weekly survey, whereas only 29.8% of the edges in the Combined Weekly Network were previously captured in the Nomination network. The numbers of reciprocal (reported by both individuals) and non-reciprocal edges for each of the ten Week Networks are shown in Fig. 7; the mean percentage of each Week's edges that were reciprocal was 43.7 (SE: 0.8). Mean indegree, outdegree, and total degree in the Nomination Network were estimated by intervention group (see Supplementary Table S7) both for all nominated individuals and for enrolled participants, as well as by enrollment type for the enrolled participants (see Supplementary Table S8). There were no major differences by intervention groups for the three degree types (in-, out-, and total) within the Nomination Network for all nominated individuals or only enrolled participants. Within the subset of enrolled participants in the Nomination Network, nominees had higher in-, out-, and total degree than seed participants, though only differences for indegree and total degree were statistically significant ($P < 0.001$ for each). Cumulative distribution curves of in-, out-, and total degree for the Nomination Network are shown in Fig. 8. The distributions of all three measures (in-, out-, and total), were heavily right-skewed and over-dispersed, with the majority of individuals having two or fewer links. Consequently, the Nomination Network appears scale-free, with a log–log plot and linear trendline ($R^2 = 0.91$) illustrating the approximately power–law distribution for total degree, as shown in Supplementary Fig. S2. The log–log plot of total degree in the Combined Weekly Network is shown in Figure S3; this plot also approximately exhibits the power–law distribution ($R^2 = 0.84$). The clustering coefficients for the full Nomination Network and restricted to only enrolled participants were 0.13 and 0.12, respectively, and the Combined Weekly Network's was 0.39. The mean clustering coefficient for the ten Week Networks was 0.27 (SE: <0.01). The transitivities of the full Nomination Network, the restricted Nomination Network, and the Combined Weekly Network were 0.005, 0.19, and 0.58, respectively.

Assortativities for the Nomination Network are shown in Supplementary Table S9. Assortativities calculated among all individuals in the network were statistically significantly positively assortative ($P < 0.002$) by intervention group, residence hall, and residence house. Fig. 9 illustrates the assortativity by residence hall, and Fig. 10 illustrates assortativity by intervention group. In the reduced network of only enrolled individuals, participants were statistically significantly positively assortative by iEpi participation status, age, gender, race, and alcohol use ($P < 0.002$).

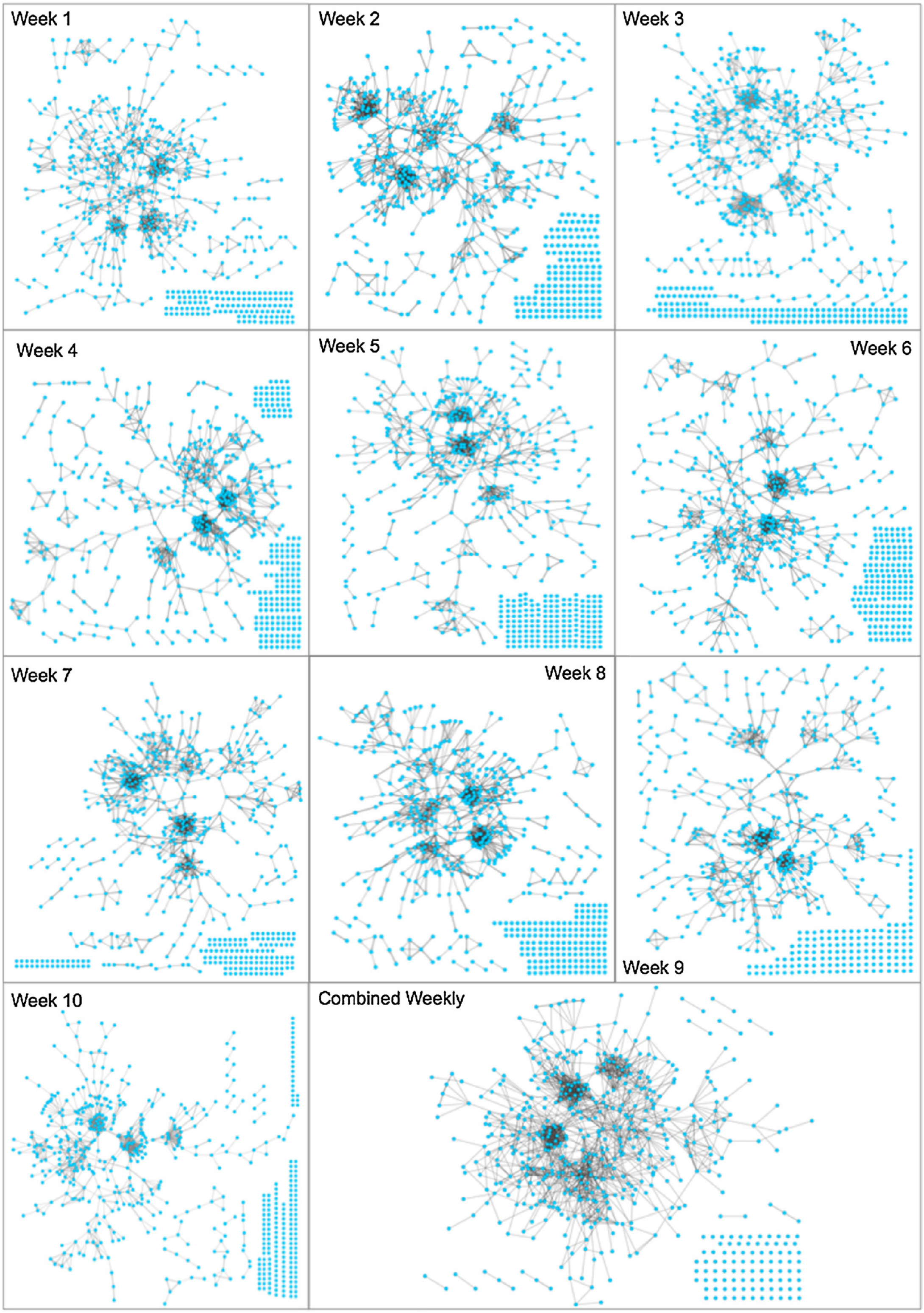

Fig. 5. *Individual Week and Combined Weekly Networks.* Each node (circle) in the network represents an enrolled participant in the eX-FLU study (N = 590) and the edges between them represent a face-to-face contact reported on a given weekly survey. In the individual Week Networks, edges are directed with an arrow from the individual who reported the contact to the participant with whom they reported contact and may be reciprocal, if both participants reported the contact. In the Combined Weekly Network, each undirected edge represents contact between two participants reported at least once during the study period, by one or both participants.

Closeness and betweenness centrality, calculated for individuals in the largest connected component in the Nomination Network (N = 1827), are shown in Supplementary Table S10. These individuals had a mean closeness of 0.13 (SE: <0.01). The mean betweenness centrality of this component was found to be <0.01 (SE: <0.01), indicating that, on average, individuals in the Nomination Network were on a very small number of unique shortest paths between two other participants.

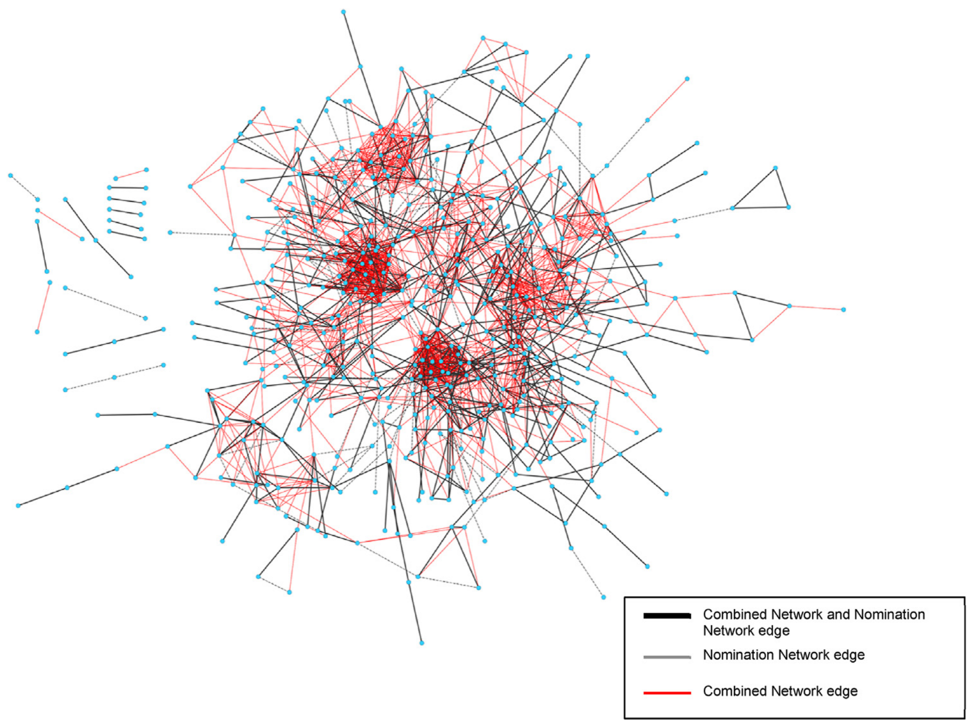

Fig. 6. *Nomination Network and Combined Weekly Network.* Each node (circle) in the network represents an enrolled participant in the eX-FLU study ($N = 532$ (excludes isolate participants)). Thick, black edges represent an edge between two participants that was both a nomination link (i.e., in the Nomination Network) as well as a face-to-face contact reported on a weekly survey (i.e., in the Combined Weekly Network) (number of edges = 556). Dotted edges were nominations between two participants that were not subsequently captured as a face-to-face contact on a weekly survey (number of edges = 99) and red edges were face-to-face contacts found in the Combined Weekly Network that were not also nominations (number of edges = 1310). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

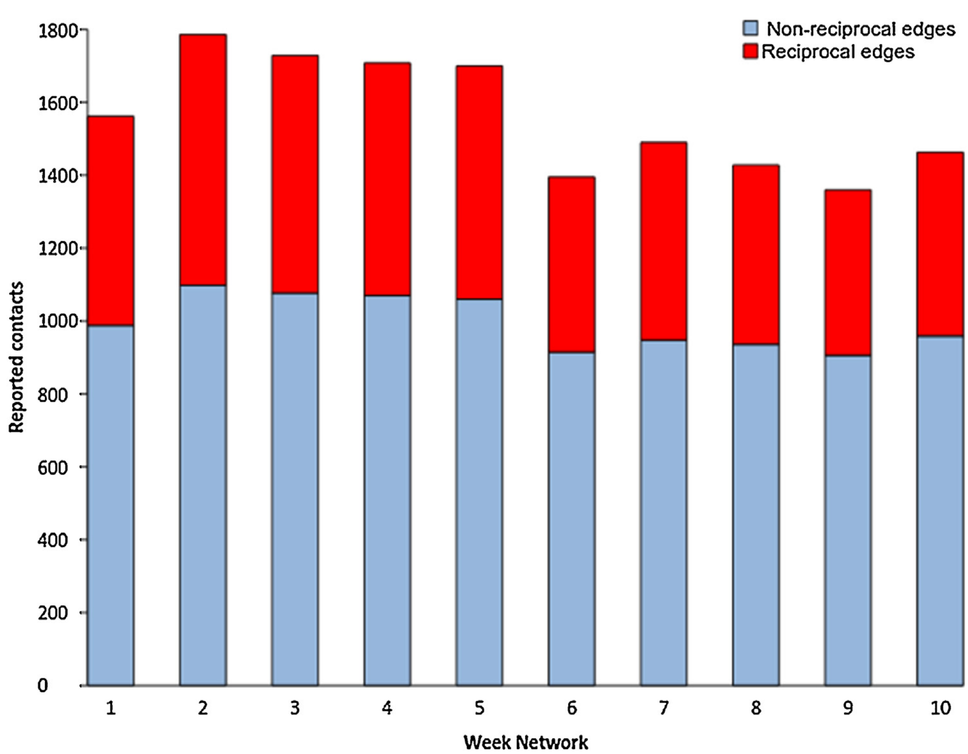

Fig. 7. Proportions of reciprocal and non-reciprocal reported face-to-face contacts in each Week Network.

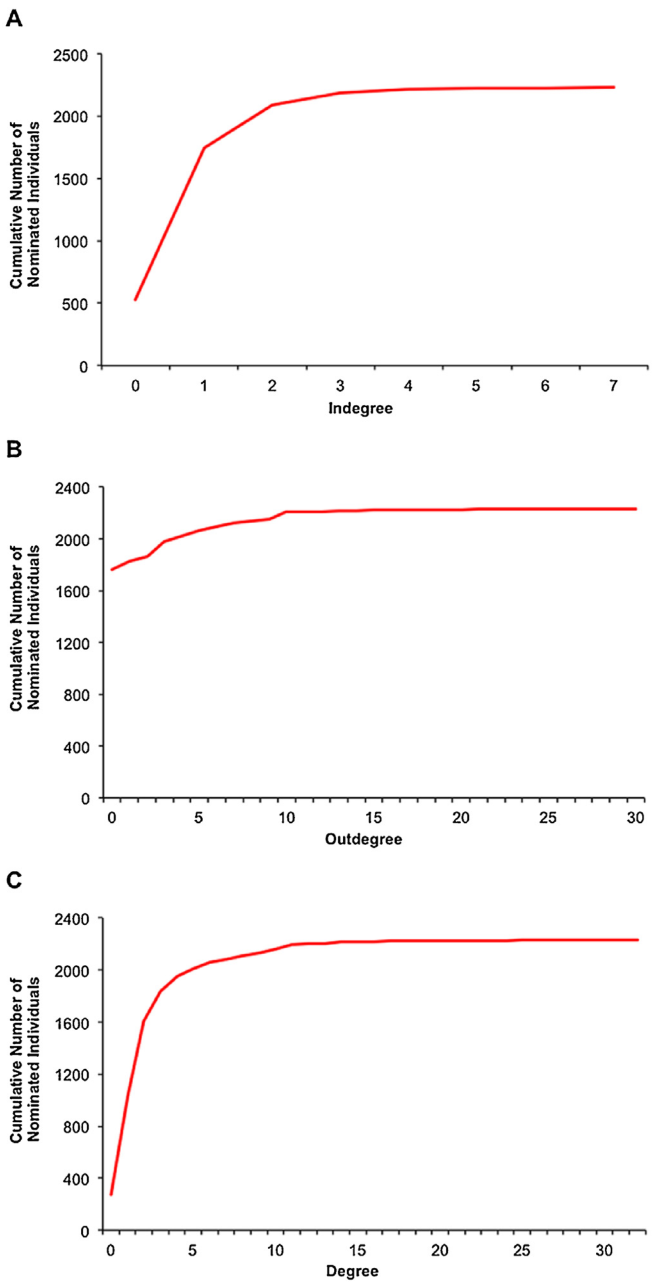

Fig. 8. *Cumulative degree distributions for the eX-FLU Nomination Network.* Cumulative number of nominated individuals by (A) indegree, (B) outdegree, and (C) total degree.

4.5. iEpi sub-study characteristics and network analysis

Of the 590 enrolled participants, 103 (17.5%) students participated in the iEpi sub-study. Thirty participants in the iEpi sub-study reported symptoms meeting the study criteria for ILI, 13 (43.3%) of which were in the 3-Day isolation intervention group. A total of 1707 contextually-based surveys were administered on all sub-study smartphones (mean 21.9/day), 1215 (71.2%) of which were responded to by iEpi sub-study participants (mean 15.8/day). A total of 82 (79.6%) participants responded to at least one contextually-based survey during the study. Participants responded to an average of 14.8 surveys (range 1–67, median 12) over the course of the study.

The demographic, health behavior, health status, and psychosocial characteristics of individuals who participated in the iEpi sub-study are shown in Supplementary Tables S11–S13. Seeds and nominees (48.5% versus 51.5%) and individuals randomized to the 3-Day intervention versus control group (47.6% versus 52.4%) were approximately evenly distributed among the iEpi sub-study participants. There were no statistically significant differences between iEpi sub-study participants and non-participants in demographics, health status, psychosocial characteristics, and the majority of health behaviors. However, there was a statistically significant difference between iEpi sub-study participants and non-participants ($P < 0.001$) in drinking behavior; a lower proportion of iEpi sub-study participants reported drinking at least one alcoholic drink per week than non-participants (21.1% versus 41.2%, respectively).

During the study period, 93 of the iEpi sub-study smartphones made Bluetooth contact with at least one other iEpi smartphone; and 93 smartphones made Bluetooth contact with other devices of any kind (including devices belonging to individuals outside the study). Over the course of the sub-study, there were a total of 453,281 Bluetooth contacts between smartphones within the iEpi sub-study, and 1591,741 total Bluetooth contacts with other devices of any kind, with each iEpi phone averaging 62.5 contacts/phone/day with study phones and 219.4 contacts/phone/day with devices of any kind, respectively. Each smartphone detected an average of 56.5 unique iEpi sub-study phones and 516.3 unique devices outside of the iEpi sub-study. iEpi smartphones also made 10,791,176 contacts with wireless internet hotspots, with each phone detecting an average of 56.4 distinct wireless internet hotspots/day. Fig. 11 shows the iEpi Bluetooth contact network, including the frequency with which individuals interacted over the entire iEpi sub-study period.

5. Discussion

We present for the first time the methods for overlaying a cluster randomized isolation intervention onto a social network sample in order to examine the effect of isolation on the transmission of influenza and other respiratory infections within a social network of students living in university residence halls. Our successful use of chain referral sampling during participant recruitment allowed us to elucidate links within a social network of individuals at baseline and then follow this dynamic social network over time during the 2013 influenza season. The chain referral method of enrollment was particularly important in our study design; by enrolling students via their social connections, we increased the likelihood of a more complete social network during the study period. Most studies that include social contact information are egocentric (i.e., they only measure the number of immediate contacts for each individual, rather than capturing the connections between individuals). However, using an explicitly social network-based enrollment approach allowed us to gather longer chains of contacts between individuals. This approach will help to reveal transmission along a chain of contacts, or effects due to intersections of multiple transmission chain; fully capturing these dynamic transmission processes as they travel along the social network requires combining a chain referral-type approach with social contact measurements over time. Our study also highlights the importance of the nomination process in subsequent participation, as students who were nominated by more enrolled participants were more likely to enroll in the study than those who received fewer nominations. This perhaps indicates that students are more likely to participate in this type of study if more of their friends are also participating. Additionally, this likely resulted in participation by more socially connected students, which is particularly important for studies of infection transmission over social networks. Further, demographic data of undergraduate students living on-campus provided by University Housing shows that our study population was representative of the university population. Our study design is well-suited for examining the impact of not

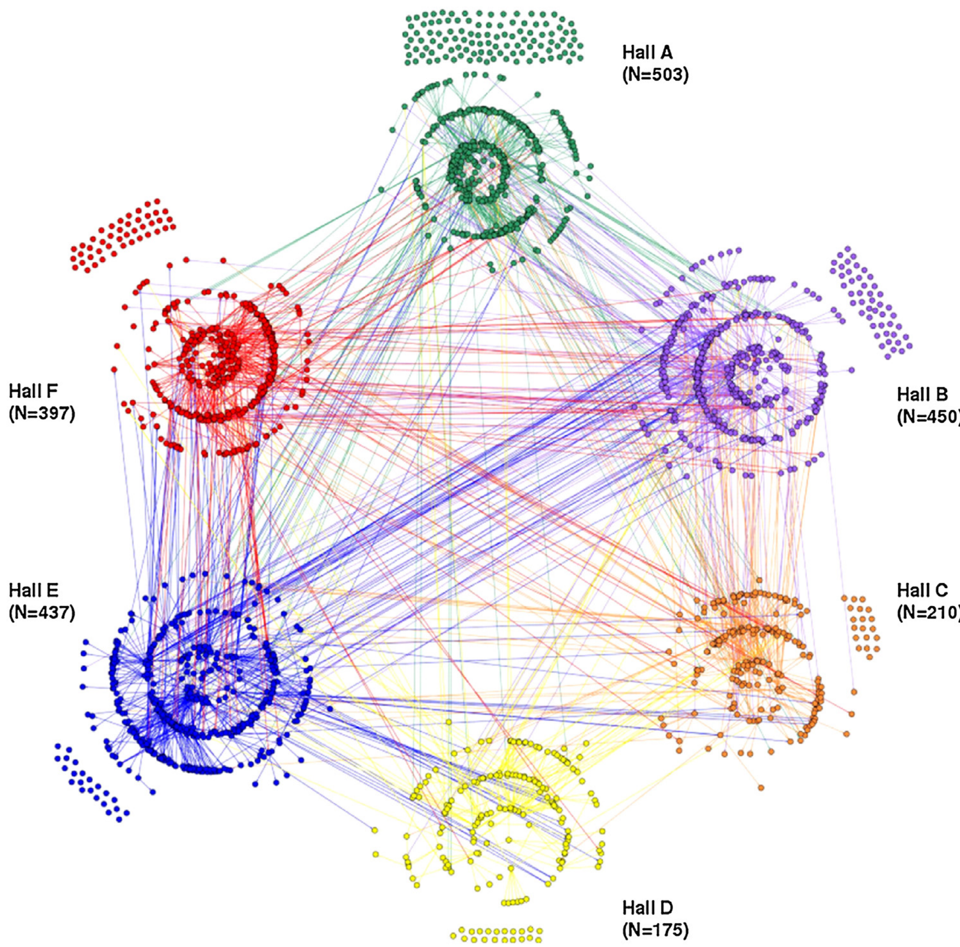

Fig. 9. *Assortativity by residence hall for the eX-FLU Nomination Network (N = 2172).* Each node (circle) in the network represents an individual nominated to join the eX-FLU study. Nodes are grouped and colored according to residence hall and colored lines represent nominations sent from residents of a particular hall. Individuals who moved out of an eligible hall prior to the intervention period (*N* = 57) were excluded. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

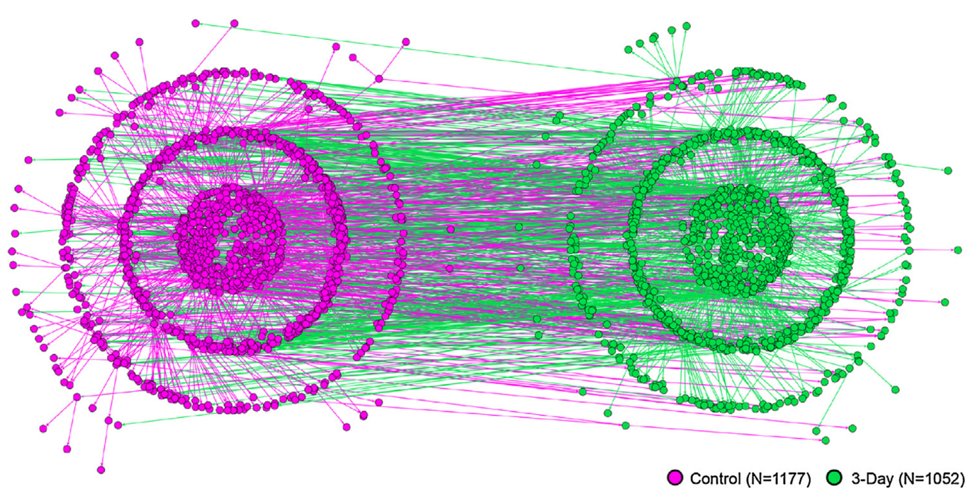

Fig. 10. *Assortativity by intervention group for the eX-FLU Nomination Network (N = 2229).* Each node (circle) in the network represents an individual nominated to join the eX-FLU study. Nodes are grouped and colored according to intervention arm (Control, 3-Day) and colored lines represent nominations sent from residents in a particular intervention group. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

only isolation on preventing influenza transmission, but also modeling the impact of other measures, such as quarantine, that rely on collecting data among healthy contacts and following them over time to examine occurrence of illness and interactions over the period of exposure to illness onset. In addition, we introduced the use of a novel smartphone application, iEpi, which collected Bluetooth data on social contacts as well as contextually-dependent, contact-triggered survey data that will allow us to gain insights into interactions between participants in our study that may not be captured using traditional social network survey methodology.

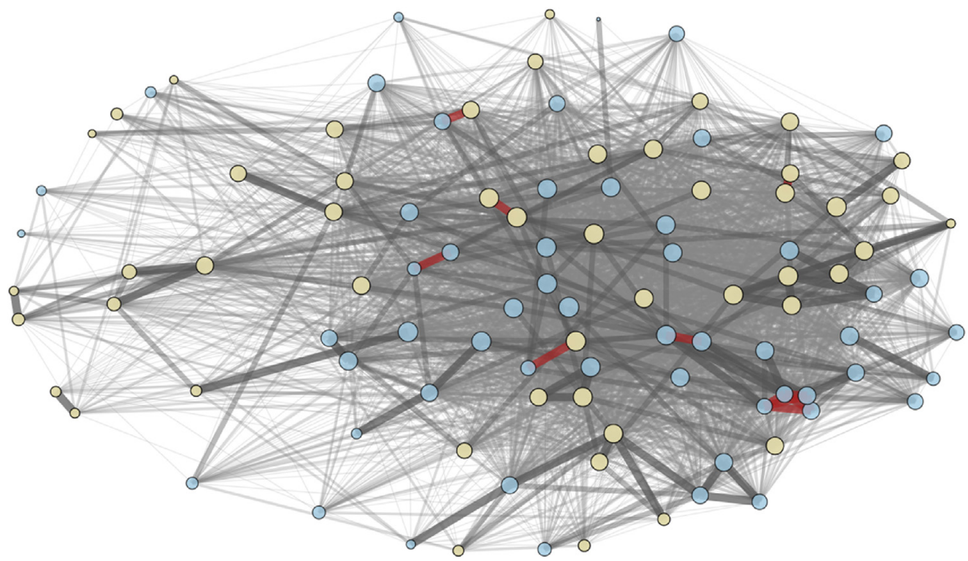

Fig. 11. *iEpi Bluetooth network (N = 103). Network of Bluetooth contacts between smartphones in the iEpi sub-study.* Each node (circle) represents an individual in the iEpi Sub-study, and the links (edges) between nodes represent Bluetooth detections between smartphones of individuals in the sub-study. Nodes are colored by intervention arm (yellow = Control, blue = 3-Day). Node size is proportional to the total number of Bluetooth detections by that individual's smartphone with any other sub-study phone, and link thickness indicates the number of Bluetooth contacts between those two nodes over the entire study (from thinnest to thickest: ≤10 contacts, 11–100 contacts, 101–1000 contacts, > 1000 contacts). A small number of individuals had over 10,000 contacts with one another, indicated by red edges. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Future analyses comparing the self-reported social network to the Bluetooth network will shed light on the accuracy and reliability of self-reported contact data. The balance of study population characteristics observed at baseline across intervention groups – combined with prospective data collection of ILI symptoms, social interactions, and isolation behavior over a 10-week intervention period – will allow us to address numerous questions related to infection transmission dynamics. In addition, we will be able to provide valuable insights regarding the interplay between social network characteristics, behaviors, and perceptions of isolation among college-aged students.

Our study builds upon previous non-pharmaceutical intervention research conducted by our research team, in which we examined the use of surgical face masks and hand hygiene for prevention of influenza among college-aged students living in university residence halls, which typically involves one to three students sharing close living quarters (Aiello et al., 2010, 2012). By conducting our study in university residence halls we were able to overcome several limitations facing studies of influenza transmission conducted in the household setting (Cowling et al., 2009; Hitomi and Shimizu, 1985; Viboud et al., 2004). First, it is logistically difficult to require symptomatic individuals within households to isolate themselves in separate living quarters in order to protect healthy family members. Second, even if it were possible to bar interaction in the household setting, the protective effects of isolation would not be easy to measure given the high rate of secondary transmission that occurs in the household setting (Cowling et al., 2009; Hitomi and Shimizu, 1985; Viboud et al., 2004). By contrast, a dorm setting allows more effective physical barring of interaction among the majority of social network members as well as classroom interactions (apart from shared bathroom facilities and possible roommate interactions during the intervention period). As an adjunct to our intervention, we provided and encouraged the donning of surgical masks when an intervention participant needed to visit the bathroom or leave their dorm room for any other reason. In addition, we provided guidelines on proper covering of coughs/sneezes and encouraged proper hand hygiene for the ILI cases and their roommates to reduce the potential for transmission when it was impossible to physically intervene on human interaction (i.e., sharing a dorm with roommates during the intervention). Third, we were able to explicitly gather extensive data on factors that are external to households but may also contribute to transmission, such as shared class schedules and participant interactions both within living quarters and within the wider university community. Overall, our study design and the physical environment of university residence halls allowed us to enumerate a much larger number of potential contacts and varying contexts where transmission may occur than one would generally observe in a household setting. That said, schools and particularly the residence hall setting are specialized environments and do not mirror the general population. However, our study setting does provide us with insights into larger networks that may be more representative of interactions that happen outside the household, in schools, and in other social settings (Ali et al., 2014; Newman and Girvan, 2004; Schafer, 2011; Zachary, 1977).

Although seeds and nominees in our study population had few differences in the demographic, health behavior, health status, and psychosocial characteristics, we identified a number of interesting features of our social network related to enrollment type. We found that nominees had higher indegree, outdegree, and total degree compared to seeds, indicating nominees were more socially connected than seed participants. In addition, nominees were slightly older than seeds. These findings are consistent with the "friendship paradox," wherein friends (i.e., nominees) named by a randomly chosen individual (i.e., a seed) tend to have, on average, more friends than the initial randomly-selected individual (Feld, 1991; Zuckerman and Jost, 2001). In addition, older participants may be more highly connected individuals because they may have been on campus for a longer period of time and may also be resident advisors who are overseeing students living in the eligible residence houses who would therefore be connected to a greater number of participants.

There were also few differences in self-reported characteristics by intervention group, suggesting that the randomization procedure was successful, although control group participants reported a lower percentage of parents with post-graduate education than the 3-Day intervention group. Similar average levels of social-connectedness, as measured by degree (in-, out-, and total) were seen between intervention groups, both when considering all members of the Nomination Network as well as among only enrolled individuals. This result again suggests successful randomization within the total population of eligible, nominated individuals as well as among those who enrolled in the study. However, we note that while the analyses of degree were adjusted for randomization-clusters, this may not be sufficient to account for the dependencies in network data. Future work using exponential random graph models (and related methods such as degree-preserving randomization methods) to account for this limitation is warranted.

There were high levels of participation and low loss to follow-up in our study. Only 12 and 11 individuals in the intervention and control arms dropped out of the study during the intervention period, respectively. However, approximately 20% of enrolled students did not participate beyond completing the enrollment process, perhaps due to the lag between the enrollment and study periods. Future studies should identify ways to encourage completion beyond initial enrollment, e.g., perhaps timing enrollment closer to the study period or providing frequent incentives based on completion of the weekly surveys. Among those who did participate during the intervention period, survey completion and active participation was high, with over eighty percent of participants completing over half of the weekly surveys. Additionally, the average number of contacts reported by individual participants per survey remained fairly consistent over the intervention period (mean: 3.6, SE: 0.06), thus we did not observe attrition in reporting of social interactions over the course of the study. As only one participant needed to report contact for the edge to be included in the Weekly social networks, we were able to capture contacts with students who were not actively participating, reducing the impact of missing data. However, close to half of all contacts reported on the weekly surveys were reciprocal (i.e., reported by both connected participants), allowing for additional verification of a given edge. Additionally, the increased participation requirements for ILI cases did not reduce engagement, as cases completed the same number of weekly surveys as non-cases. Similarly, intervention arm did not significantly affect participation among ILI cases, as demonstrated by the fact that 3-Day ILI cases had similar participation rates as control ILI cases. These results suggest that students did not find the weekly surveys, additional ILI surveys, specimen collection, and isolation to be overly onerous, and that it did not differ by intervention arm.

We observed moderate to high assortativity by residence hall and residence house among all nominated individuals, which is expected, as people who live close together may be more likely to nominate each other to join the study. Given that intervention groups were assigned by cluster, which were determined in large part by geographic boundaries within residence halls, it is also not surprising that we identified significant, moderate assortativity by intervention group for the Nomination Network. Within the reduced network of enrolled participants who provided self-report information, participants also tended to associate with those who shared sociodemographic characteristics such as age, sex, race, parental education, and employment, as well as those with similar health habits (i.e., smoking, drinking behavior, and risk for complications due to an influenza infection), which is consistent with previous studies demonstrating that health behaviors cluster within social networks and that individuals tend to have friends with similar demographic profiles (Barclay et al., 2013; Barnett et al., 2014). The iEpi sub-study participants were less likely to engage in drinking than non-participants, which may reflect the sampling method employed for selection into the iEpi sub-study, whereby individuals from a strongly inter-connected community were given priority for invitations to participate in the sub-study as highly connected individuals are likely to share health behaviors that were positively assortative in the Nomination Network. However, given the lack of statistically significant differences between iEpi sub-study and non-iEpi participants for other demographic, behavioral, and psychosocial characteristics, this result may simply be by chance, or may indicate that among those targeted to participate there was selection by nondrinkers.

Contact mixing patterns, specifically, numbers of contacts and clustering, are particularly important to airborne pathogen spread (Edmunds et al., 2006, 1997; Melegaro et al., 2011; Wallinga et al., 1999; Mossong et al., 2008; Eames et al., 2010; Van Kerckhove et al., 2013; Read et al., 2008). In terms of overall network structure, the average closeness and betweenness centralities for the largest component in the Nomination Network were both low, with small standard deviations, suggesting that most individuals were not strongly central to the network. The generally low betweenness centrality for most individuals implies that there were multiple shortest paths between most individuals, forming a more evenly dense network as opposed to a network wherein a small number of individuals act as "bridges" between more densely-connected clusters or clumps within the fully connected network. As such, it may difficult or impossible to identify individuals who are particularly influential in transmission across the network. The degree distribution for the overall Nomination Network and Combined Weekly Network were scale-free with a roughly power–law degree distribution (Supplementary Figs. S2 and S3), consistent with a wide range of previous social network studies (e.g., (Barabási, 2009; Barabási and Albert, 1999; Newman, 2001)). Scale-free degree distributions have been shown to facilitate rapid dispersal of information (or in this case, infection), across the network and to have connectivity that is robust to random node removals (Barabási, 2009; Lusseau, 2003). We also observed positive clustering coefficients in both the Nomination and Week Networks, which is an additional measure of the degree of network clustering. Transitivities were higher in the Combined Week Network than in the Nomination Network. Clustered network structures such as these have been shown to facilitate rapid dispersal across the network in the first wave of an infection, although they may inhibit subsequent waves of infection (Kiss et al., 2006). As the majority of the Nomination Network was subsequently captured in the Combined Weekly Network, it appears that the students maintained their relationships from early in the school year as well as added new relationships. This overlap between the Nomination Network and Combined Weekly Network show that "early" networks could potentially be used to preliminarily identify structures and individuals that might later facilitate or inhibit transmission during the influenza season. Further analyses on the dynamic social network captured during the study period will be discussed in future papers.

To the best of our knowledge, eX-FLU is the largest time-varying college-student social network dataset to date. However, there are static network studies of similar size to ours with which we can compare our baseline Nomination Network. For example, Christakis and Fowler (2010) used a sample of 744 undergraduate students enrolled via chain-referral; they reported an average number of nominations per student of 2.8, which is lower than the mean number of nominations sent per participant in our study (4.0 (SE: 0.2); see Table S7) but could be used to make comparisons regarding network features of the two studies. In Barnett et al. (2014), a smaller network of 129 students living on-campus had an average nomination outdegree of 4.1, which is more similar to our results.

The data collected on the enrollment, baseline, weekly, and ILI-related surveys were self-reported, and participant responses may be susceptible to recall bias. The duration of time participants were asked to recall information on the weekly surveys was, however, limited to the past seven days; on ILI-related surveys, it was limited to the past three days. The iEpi sub-study social network data was frequently sampled, as the iEpi phones collected data in five-minute intervals that can be used to verify and fill in gaps in the survey-based social network data collected in our study. We acknowledge, however, that the social network captured by surveys and iEpi data together represents only a fraction of the participants' full network of social contacts. This may be partially mitigated by examining the iEpi smartphone detection of Bluetooth devices outside of our study, which will allow us to approximate the overall number and frequency of social contacts iEpi sub-study participants had outside of the study. Although there are potential shortcomings in our social network analysis, the combination of survey and electronic monitoring has provided us with a more complete picture of network evolution during sequestration than any studies to date.

The intervention used in our study was un-blinded, and this may have biased self-reports of ILI. For example, participants randomized to the 3-Day isolation intervention group who were unwilling to sequester themselves while ill may have chosen not to report their symptoms to study staff as often as control participants. However, ILI reporting bias was likely minimal based on our initial analyses in which we detected a similar incidence of ILI in both study groups (16.2% of intervention participants and 21.3% of control participants). In addition, participants were made aware of all study protocols to which they could be randomized prior to consent, which we anticipated would increase the likelihood that individuals who enrolled were willing to participate in either the 3-Day isolation intervention or control group. We also provided a wide range of services for those in the intervention group to facilitate compliance with isolation, including delivering snacks during their isolation period, such as doctors' notes to instructors or employers to excuse participants from classes or work, and assistance with obtaining class notes or proctoring of exams falling during intervention group participants' isolation period. In addition, each participant received a kit that included facemasks to be worn if they needed to leave their room during their isolation period, a thermometer for verifying fever, and hand sanitizer. Importantly, isolation was voluntary, as per the human consent process, and compensation was not compliance-dependent, therefore potential biases related to participants' self-reporting of intervention compliance were likely minimized. In future analyses, we will be able to compare the self-reported isolation behavior among the subset of ILI cases who participated in the iEpi sub-study to the objectively measured data collected by the iEpi application, allowing us to assess the degree of reporting bias present among this subset of individuals in our study.

This study presented a number of challenges. The size of the study, as well as the setting, required extensive organizational efforts. For example, a large study staff had to be trained in recruitment, participant assistance (e.g., illness response, food delivery during isolation, and follow-up communication), online survey development, database creation and management, specimen collection, data cleaning and analysis. The complexity and amount of the collected data required a large amount of server space, as well as a programming specialist to create a system that could automatically make live updates, email and schedule specimen collection, identify and email contacts of ILI cases, and link data across the various surveys. Additionally, the iEpi sub-study required extensive mapping of on-campus routers, occasional debugging, data cleaning and verification. The study population and setting also added to the logistical challenges of the study. Study staff needed access to the residence halls for recruitment and specimen collection, which required cooperation with multiple university offices (Housing and Security). Data cleaning was extensive, particularly coding any open ended survey responses, filling in class schedule responses, and deciphering the large amount of iEpi data to ensure the smartphones were collecting data accurately and consistently (e.g., using the correct timestamps and locations). The overall success of the recruitment, survey, and intervention methods leads us to conclude that if we were to later run a similar study, we would be able to use this study protocol without making substantive changes. To the best of our knowledge, the information in this study represents the most comprehensive longitudinal data collected in a social network study of respiratory infection transmission to date. Participant feedback on the eX-FLU study was also largely positive. The monetary incentive provided was successful in motivating participants to join the study, with 95.2% of those who completed the exit survey ($N = 295$) reporting the cash incentive as a reason for joining the study. In addition, 96.5% ($N = 278$) of participants who responded to the exit survey reported they would be willing to participate in a similar study in the future. These findings suggest that the methodology used is practical for future studies and the monetary incentive was sufficient to promote participant enrollment. Moreover, given the wide array of self-reported and objective data collected in this study, we will be able to address numerous questions related to social network interactions, behaviors, and infection transmission in future work. For example, analyses of the data derived from this study may provide insights on how health behaviors such as hand hygiene are transmitted along social networks and how these behaviors may be modified by illness status. These data may also allow us to conduct analyses to assess what role an individual's position in the social network may play in their health behaviors. In addition, data on different types of viral and bacterial pathogens, viral shedding, bacterial colonization, and transmission of viral and bacterial pathogens to healthy contacts will help elucidate the occurrence, transmission, and co-infection of specific types of viruses and bacteria over time, and to generate transmission trees (Ypma et al., 2012). Furthermore, our assessment of bacterial colonization using specimens collected from healthy contacts in our study will allow us to fill gaps in the literature regarding colonization in young adults who reside in community settings, as most previous studies have focused on very young populations (Rodrigues et al., 2013; Sá-Leão et al., 2008), elderly populations (Videcnik Zorman et al., 2013), or individuals in health care centers (Peleg and Hooper, 2010). Moreover, while this study had a specific focus on the effects of isolation, the underlying network data can be used to develop simulation models of social network dynamics among college students, to address a range of other questions. For example, one might examine via simulation the effects of quarantine (the restriction of movement of individuals whom have been exposed to an infectious illness without signs of illness) rather than isolation. In general, there is a need for more work on examining the effects of behavior (for both susceptible and infected individuals) in mathematical epidemiology (Funk et al., 2010, 2015; Phua and Lee, 2005; Hayashi and Eisenberg, 2016) This study will provide a new resource for these efforts building on egocentric data on social mixing patterns that have been used in previous work (Mossong et al., 2008; Potter et al., 2011; Hens et al., 2009; Fu, 2005; Mikolajczyk and Kretzschmar, 2008).

In conclusion, this is the first study design to overlay a randomized isolation intervention onto a social network populated via chain referral sampling and to prospectively collect data on social interactions, ILI, and isolation behavior in a population at risk for influenza in the case of a pandemic. The data obtained from this study, including the use of novel cell phone technologies for examining human interactions and behaviors, present an unprecedented opportunity to test and assess various aspects of infection transmission, as well as clustering and transmission of socio-behavioral characteristics, viral shedding over time, and interventions targeted within social networks. Further analyses will provide key insights regarding the impact of isolation on the prevention of influenza transmission as well as many other respiratory viruses that share similar transmission pathways. Finally, we plan to provide these data in an open access format in the future to allow other researchers to utilize them for mathematical modeling applications and continued study of the impact of non-pharmaceutical interventions for reducing the transmission of infectious diseases in the community setting. Currently, the data is identifiable and requires several steps to provide de-identified data. We plan to work with interested investigators on a case by case basis to help them with accessing the data after de-identification so that our provision of data meets our ethics requirements for the study confidentiality.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.epidem.2016.01.001.

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