Tracking Invasive Extraintestinal Pathogenic *E. coli* Disease in Older Adults in a Community-Based Clinical Trial Setting: EXPECT-1 Study

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KEY FINDINGS STATEMENTS

- In a population of 4470 community-dwelling older adults, including 59.5% of those with a history of urinary tract infection (UTI) in the previous 10 years, 4 participants developed invasive extraintestinal pathogenic *Escherichia coli* disease (IED) through 12 months of follow-up
- 4 IED events were captured through deployment of different tracking methods: a self-report (n=2), a general practitioner (GP) report (n=1), and a 4-month follow-up call by the local research team (LRT; n=1)
- The incidence rate of IED was 98.6 events per 100,000 person-years. In participants with a history of UTI, the incidence rate was 164.4 events
- Of detected hospital admissions, 56.6% were reported by the site and 48.7% were self-reported by participants
- In a US-based substudy, a smartphone-based geofencing app captured 72 hospitalizations

CONCLUSIONS

- Detection of IED events in a community setting can be maximized through the combined use of participant self-report, GP report, and phone-based follow-up. The addition of geofencing may enhance IED catchment efficiency
- Findings from the EXPECT-1 study provided insight into the feasibility of executing the ongoing phase 3 trial (NCT04899336) to evaluate the efficacy of a novel vaccine against IED (ExPEC9V) in community-dwelling older adults with a history of UTI in the previous 2 years

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INTRODUCTION

- Pathogenic strains of *E.coli* can cause a wide range of invasive diseases[1] that can be collectively described as invasive extraintestinal pathogenic *E. coli* disease, also known as invasive *E. coli* disease (IED)
  - IED is defined as an acute illness consistent with systemic bacterial infection microbiologically confirmed by a positive *E. coli* culture either from a normally sterile body site (including blood) or urine in patients with urosepsis and no other identifiable source of infection[2]
- Older adults might have an increased risk of developing IED[3]
- A novel ExPEC9V vaccine to prevent IED in older adults (aged ≥60 years) is currently being evaluated in a phase 3, double-blind, placebo-controlled randomized trial (*E.mbrace;* NCT04899336)[4]
  - The performance of such a trial to detect IED events depends on the use of a sufficiently large sample size as well as efficient tracking of hospitalizations and medical encounters, and might be enhanced by utilizing novel tracking technologies such as smartphone-based geofencing[5]

OBJECTIVES & ENDPOINTS

- The EXPECT-1 study (NCT04087681) evaluated the feasibility of capturing IED events as well as hospital admissions and medical encounters among community-dwelling adults aged ≥60 years
  - The key endpoints were the incidence of IED and the number of hospital admissions and medical encounters as reported by the 2 sources: the site and participant self-report

METHODS

- Prospective observational study conducted in 8 hospitals in Canada, United States, France, Germany, Italy, Spain, United Kingdom, and Japan
- Eligible patients were aged ≥60 years and deemed to be in stable health; ≥50% of participants were required to have a history of UTI in the previous 10 years
- Recruitment was performed through database screening by GP and primary care centers and was supported by the LRT, collectively referred to as the "site"
- The follow-up duration was 12 months
- Patient referrals were tracked by the site. Additionally, participants were asked to inform the site in case of a hospital admission
- IED events were diagnosed through medical judgment based on the treating physicians' notes and *International Classification of Diseases* codes, which include culture-confirmed bacteremia and sepsis
- Cumulative incidence and incidence rate of IED were estimated
  - Cumulative incidence is a ratio of the total number of IED events to the total number of enrolled participants; 95% confidence intervals (CIs) were based on the exact Clopper-Pearson interval
  - Incidence rate is a ratio of the total number of IED events to the total length of IED-free follow-up time; 95% CIs were based on the exact Poisson interval
- A US-based substudy evaluated the usefulness of the geofencing app to electronically track hospitalizations

RESULTS

Baseline characteristics

- In total, 4470 participants were enrolled (full analysis set [FAS]; **Table 1**)
  - 59.5% (2657/4469) of participants had a history of UTI in the past 10 years
- A history of IED in the past 10 years was reported in 7.2% (324/4469) of participants
- Most participants (94.4%) had a medical comorbidity
  - The most common comorbid condition was cardiovascular disease (64.9%), followed by endocrine and metabolic (46.8%), musculoskeletal (43.4%), genitourinary (31.2%), and gastrointestinal disease (26.9%)

TABLE 1: Summary of key baseline characteristics, FAS

	IED	All participants
FAS, n	4	4470
Age, y	4	4469
Mean (SD)	72.0 (12.03)	70.5 (7.10)
Median	70.5	70.0
Range (min, max)	(60, 87)	(60, 96)
60–74	50.0% (2)	72.1% (3220)
75–84	25.0% (1)	23.9% (1069)
≥85	25.0% (1)	4.0% (180)
Sex	4	4469
Female	100.0% (4)	68.0% (3040)
Ethnicity	2	3703
African	0	4.7% (175)
Asian	0	20.6% (761)
Hispanic or Latino	0	0.2% (7)
White	2 (100.0%)	74.4% (2756)
Not reported	2	767
Living status (previous 12 months)	4	4469
At home	100.0% (4)	99.7% (4454)
Long-term care facility	0	0.1% (3)
Assisted-living facility	0	0.1% (3)
Other	0	0.2% (9)

Percentages are based on n with nonmissing values.

IED events

- 4 IED events were identified through participant self-report (n=2), a GP report (n=1), and active follow-up calls performed by LRT every 4 months (**Table 2**)
  - 1 IED event was reported outside the participating hospitals
- All IED events were *E. coli* bacteremia (**Table 2**) and occurred in females
- All patients with an IED event had a history of UTI in the previous 10 years

TABLE 2: Catchment process and clinical manifestation of IED events

IED event catchment details	UTI signs & symptoms	IED signs & symptoms	SIRS criteria	qSOFA criteria	SOFA criteria
IED event 1 (France) GP was informed of IED via hospital discharge letter. GP contacted LRT	NA	• Fever • General symptoms[a] • Abnormal MAP (mm Hg) • Laboratory values indicating bacterial infection/inflammation	1	0	1
IED event 2 (France) Participant informed EXPECT-2 PI of participation in EXPECT-1. PI contacted LRT	NA	• Fever • Tachycardia (heart rate >90 bpm) • General symptoms[a] • Nausea and/or vomiting • Abnormal MAP (mm Hg) • Laboratory values indicating bacterial infection/inflammation	2	0	1
IED event 3 (Italy) Participant informed physician in hospital about participation in EXPECT-1. Physician contacted LRT	• Dysuria • Flank pain	• Tachypnea (respiratory rate >20 breaths per min) • Abnormal WBC count (leukocytosis, ≥12× 10^9/L) • Abnormal MAP (mm Hg) • Laboratory values indicating bacterial infection/inflammation	2	1	1
IED event 4 (Italy) At the FU call on day 240, LRT was informed by participant of hospital admission due to IED	• Flank pain	• Abnormal WBC count (leukocytosis, ≥12×10^9/L) • Laboratory values indicating bacterial infection/inflammation	1	0	0

[a]General symptoms include malaise, fatigue, muscle pain, and chills. bpm, beats per minute; EXPECT-2, a second in the series of COMBACTE-NET studies to collect information about IED (NCT04117113); FU, follow-up; MAP, mean arterial pressure; PI, principal investigator; SIRS, systemic inflammatory response syndrome; SOFA, sequential organ failure assessment; qSOFA, quick SOFA; WBC, white blood cell.

Incidence of IED

- The cumulative incidence of IED was 0.09% (95% CI, 0.024–0.229%)
- The incidence rate of IED was 98.6 events per 100,000 person-years (95% CI, 25.6–248.4)
- In participants with a history of UTI in the previous 10 years, the cumulative incidence of IED was 0.15% (95% CI, 0.041–0.385%), and the incidence rate was 164.4 events per 100,000 person-years (95% CI, 43.8–420)

Treatment of IED events

- Antibiotics prescribed for the treatment of IED (data available for 3 patients) were intravenous (IV) meropenem followed by oral ciprofloxacin (n=1); IV piperacillin–tazobactam followed by IV amoxicillin–clavulanate and oral amoxicillin–clavulanate (n=1); IV ceftriaxone followed by oral norfloxacin (n=1)

Hospital admissions and medical encounters (FAS)

- The rate of hospital admissions was 56.6% (2529/4470) when reported by the site and 48.7% (2177/4470) when self-reported by participants
- The rate of medical encounters was 84.1% (3759/4470) when reported by the site and 77.9% (3480/4470) when self-reported by participants

Hospital admissions and medical encounters (patients with IED)

- Hospital admissions were reported in all IED patients by both sources
- Medical encounters were reported in all IED patients by both sources (**Table 3**)
  - Inpatient department was the most common medical encounter setting
  - All IED patients had a procedure/intervention performed during the medical encounter

TABLE 3: Medical encounters of patients with an IED event

	Reported by the site	Reported by participants
FAS, n	4470	4470
No. of patients with any medical encounter	0.1% (4)	0.1% (4)
Type of medical encounter, per patient	4	4
Hospital inpatient department	100% (4)	75% (3)
Hospital outpatient department	100% (4)	50% (2)
GP/family doctor	50% (2)	100% (4)
Emergency department	25% (1)	0
Para-medical services	0	25% (1)

Participants are counted only once for any given category but may appear in multiple categories.

Geofencing substudy

- Between March 23, 2020 (geofencing first available for consent) and May 21, 2021 (date of last visit), 334 participants consented to EXPECT-1
  - Of those, 151 (45%) consented to the geofencing substudy, 60 (18%) signed up to use the geofencing app, and 40 (12%) logged into it
- In total, geofencing detected 72 hospitalizations
  - All events were closed by site staff after patient follow-up to confirm no infection

LIMITATIONS

- Generalizability of the findings on IED characterization and treatment is limited due to detection of 4 IED events
- COVID-19 impacted enrollment, and less data were available to reach the study objectives
- Some IED cases might have been missed as no real-time tracking of participants developing IED was deployed
- An uptake of the geofencing app among older adults was limited by difficulties in downloading the app, data privacy concerns, and the lack of hands-on support from the site due to COVID-19

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