Tufts University | School of Medicine

SITA 14° CONGRESSO NAZIONALE
GENOVA | 21-22 novembre 2024

Le infezioni comunitarie: Nuovi studi, nuove pratiche

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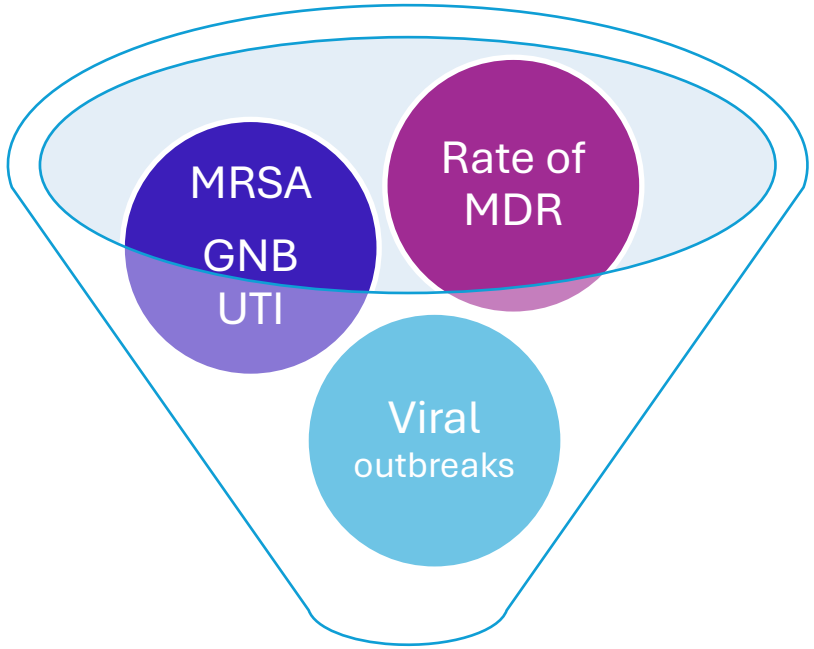
Community acquired infections

Grajales Beltrán AG et al. Vaccines 2023

Cap 805.66 per 100.000 inhabitants

Endocarditis 10 per 100.000 inhabitans

CA- bacterial meningitis 2 per 100.000 inhabitants



Breaking the DOGMA of CA infections

Epidemiology of Sepsis in US Children and Young Adults

Magil S et al OFID 2023

- 736 patients in 26 hospitals
- 60.1% had underlying conditions.
- 83.3% had community-onset sepsis

Infection Type	Total (N = 736)
Pneumonia	193 (26.2)
Documented as the cause of sepsis	152/193 (78.8)
Bloodstream	154 (20.9)
Documented as the cause of sepsis	123/154 (79.9)
Undetermined or unknown[c]	107 (14.5)
Documented as the cause of sepsis	72/107 (67.3)
Urinary tract	101 (13.7)
Documented as the cause of sepsis	77/101 (76.2)
Lower respiratory (other than pneumonia)	84 (11.4)
Documented as the cause of sepsis	36/84 (42.9)
Ear, eye, mouth, nose, or throat	64 (8.7)
Documented as the cause of sepsis	36/64 (56.3)
Skin or soft tissue	51 (6.9)
Documented as the cause of sepsis	29/51 (56.9)
Gastrointestinal tract (other than CDI)	50 (6.8)
Documented as the cause of sepsis	36/50 (72.0)
Intra-abdominal	39 (5.3)
Documented as the cause of sepsis	27/39 (69.2)
Central nervous system	36 (4.9)
Documented as the cause of sepsis	27/36 (75.0)
CDI	19 (2.6)
Documented as the cause of sepsis	5/19 (26.3)

Diagnostic Stewardship in Community-Acquired Pneumonia With Syndromic Molecular Testing: A Randomized Clinical Trial

Markussen et al JAMA Network Open 2024

- Parallel-arm, single-blinded, single-center, randomized clinical superiority trial
- Adult patients who presented to the ED with suspected CAP were recruited.
- Primary outcome: time provision of pathogen-directed treatment based on a relevant microbiological test result
- 347 enrolled : 35.3% in the intervention arm vs. 13.4% in the standard-of-care arm received pathogen directed treatment
    - reduction in absolute risk of 21.9% (95% CI, 13.5-30.3) and OR for the intervention arm of 3.53 (95% CI, 2.13-6.02; P < .001).

	Intervention arm, No. (%) (n = 97)	Standard-of-care arm, No. (%) (n = 103)	Intervention vs standard of care[a]		
			Difference, % (95% CI)	Ratio (95% CI)	*P* value
Outcomes on provision					
Any antibiotics	93 (95.9)	98 (95.1)	0.7 (−5.0 to 6.5)	OR: 1.19 (0.30 to 4.92)	.80
Pathogen-directed treatment	46 (47.4)	16 (15.5)	31.9 (19.7 to 44.0)	OR: 4.90 (2.57 to 9.77)	<.001
Continuation of appropriate empirical treatment	16 (16.5)	7 (6.8)	9.7 (0.9 to 18.5)	OR: 2.66 (1.07 to 7.33)	.03
Escalation from narrow-spectrum to more broad-spectrum treatment	14 (14.4)	4 (3.9)	10.5 (2.6 to 18.5)	OR: 4.04 (1.37 to 15.14)	.009
De-escalation from broad-spectrum to more narrow-spectrum treatment	10 (10.3)	5 (4.9)	5.5 (−1.9 to 12.8)	OR: 2.21 (0.74 to 7.52)	.14
Initiated pathogen-directed antimicrobial treatment, without prior empirical antibiotic treatment	6 (6.2)	0	6.2 (1.4 to 11.0)	NA	.01
Narrow-spectrum antibiotics within 48 h	81 (83.5)	87 (84.5)	−1.0 (−11.1 to 9.2)	OR: 0.93 (0.43 to 1.99)	.85
Single dose of antibiotics only	4 (4.3)	0	4.3 (0.2 to 8.4)	NA	.04
Antibiotics not used for more than 48 h[b]	14 (14.4)	22 (21.4)	−6.9 (−17.5 to 3.6)	OR: 0.62 (0.29 to 1.29)	.21
Treatment with intravenous antibiotics[b]	66 (68.0)	75 (72.8)	−4.8 (−17.4 to 7.8)	OR: 0.79 (0.43 to 1.46)	.46
Outcomes on duration					
Provision of any antibiotics during hospitalization, median (IQR), d	4.0 (2.9 to 6.0) (n = 93)	3.9 (2.1 to 6.1) (n = 98)	0.4 (−0.4 to 1.1)	Ratio of medians: 1.04 (0.87 to 1.25)	.63
Provision of intravenous antibiotics, median (IQR), d	3.3 (2.6 to 5.7) (n = 85)	3.1 (2.1 to 5.0) (n = 93)	0.3 (−0.5 to 1.0)	Ratio of medians: 1.08 (0.86 to 1.34)	.51
Provision of broad-spectrum antibiotics, median (IQR), d	3.8 (1.6 to 5.9) (n = 37)	3.9 (3.0 to 8.8) (n = 25)	−1.3 (−2.9 to 0.3)	Ratio of medians: 0.68 (0.42 to 1.10)	.11
Time to administration of antibiotics, median (IQR), h	2.1 (1.3 to 3.7) (n = 93)	2.1 (1.1 to 3.8) (n = 98)	0.26 (−0.60 to 1.12)	Ratio of medians: 1.14 (0.90 to 1.44)	.55
Turnaround time, median (IQR), h	4.0 (3.6 to 4.5)	68.2 (38.3 to 95.0)	−53.8 (−48.7 to −59.5)	Ratio of medians: 0.07 (0.06 to 0.08)	<.001

Lower Mortality in Patients Treated with Hydrocortisone for Severe Community-Acquired Pneumonia

Int Care Med 2022; C*hest* 2023; NEJM 2023

A randomized, controlled trial of patients with severe CAP showed no benefit for steroids

A meta-analysis of 16 randomized trials showed no effect on mortality .

Patients treated with corticosteroids were less likely to need intubation

Lower Mortality in Patients Treated with Hydrocortisone for Severe Community-Acquired Pneumonia

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Dequin et al NEJM 2023 : randomized 800 patients admitted to the ICU with sCAP to receive hydrocortisone (intravenous 200 mg daily) or placebo. Patients began treatment <24 hours of developing severe CAP and were treated for 4 days and then tapered over 4 or 10 days depending on clinical improvement.

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About one quarter of patients were intubated at enrollment, and 40% were receiving high-flow nasal cannula oxygen.

Mortality at 28 days was significantly lower with hydrocortisone than with placebo (6% vs. 12%); this benefit persisted at 90 days.

The hydrocortisone group was also less likely to require mechanical ventilation and less likely to develop shock.

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About one quarter of patients were intubated at enrollment, and 40% were receiving high-flow nasal cannula oxygen. No standardized microbiologic investigation was done.

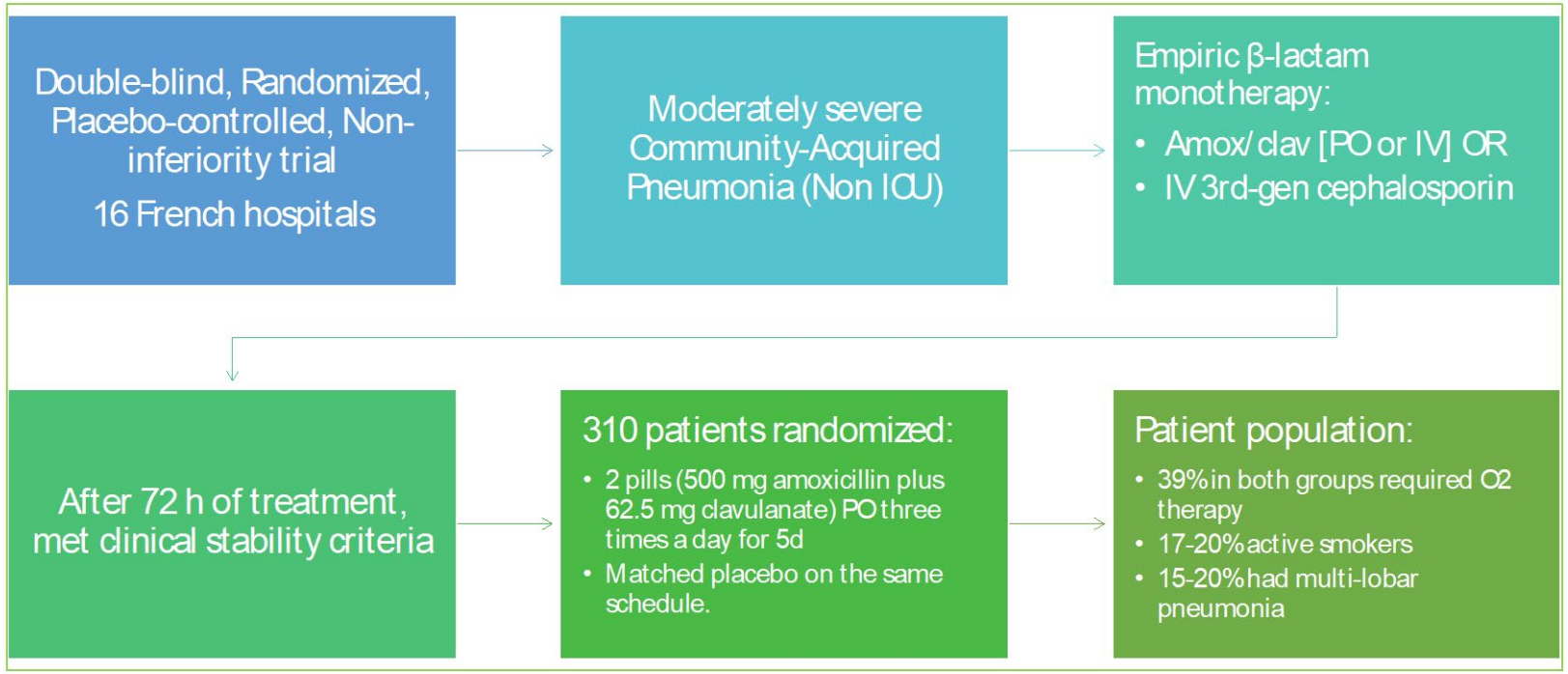
Mortality at 28 days was significantly lower with hydrocortisone than with placebo (6% vs. 12%); this benefit persisted at 90 days.

The hydrocortisone group was also less likely to require mechanical ventilation and less likely to develop shock.

Completely reconciling this body of literature is hard, but it seems that glucocorticoids lower the need for mechanical ventilation in patients with severe CAP — an outcome that reasonably could drive a mortality benefit.

Discontinuing β-lactam treatment after 3 days for patients with community-acquired pneumonia in non-critical care wards(PTC): a double-blind, randomised, placebocontrolled, non-inferiority trial

Dinh et al Lancet 2021



- Cure at day 15 occurred in 117 (77%) Vs. 102 (68%) (between-group difference of 9·42%, 95% CI –0·38 to 20·04), indicating non-inferiority.
- **Discontinuing β-lactam treatment after 3 days in patients with CAP clinically stable resulted in outcomes that were similar and non-inferior to those in patients who continued their treatment for an additional 5 days.**
- **Limits:** severe CAP, advance renal failure, absence of clinicial stability ad day 3, no focus on etiology (viral could be included)

Oral Antibiotics in Clinical Development for Community-Acquired Urinary Tract Infections

Veeraraghavan et al Inf Dis Ther 2021

- Oral carbapenems (tebipenem and sulopenem) and oral cephalosporin/b- lactamase inhibitor combinations are in various stages of clinical development for treating UTIs.
- Tebipenem and Sulopenem have completed phase III trials.
- Combinations cefpodoxime/ETX0282, ceftibuten/VNRX-7145, and ceftibuten/ QPX7728 are in phase I development.

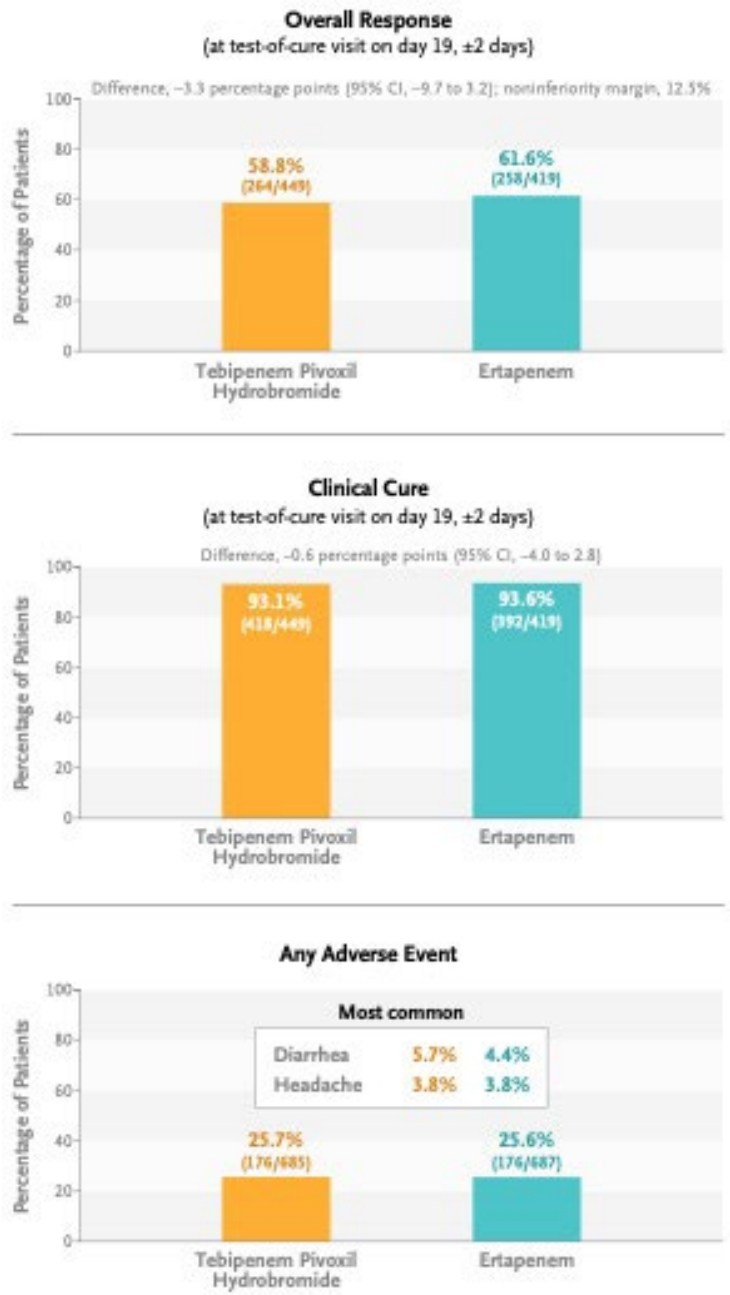
Oral antibiotics	Activity spectrum				
	ESBLs	ampC	CRE		
			KPC	MBL	OXA-48-like
Tebipenem pivoxil hydrobromide	✔	✔	X	X	X
Sulopenem-etzadroxil/probenecid	✔	✔	X	X	X
Cefpodoxime/ETX0282	✔	✔	✔	X	✔
Ceftibuten/VNRX-7145	✔	✔	✔	X	✔
Ceftibuten/ARX1796	✔	✔	✔	X	✔
Ceftibuten/ QPX7728	✔	✔	✔	✔	✔

✔ active, *X* not active, *ESBL* extended-spectrum ß-lactamases, *ampC* class C cephalosporinase, *KPC K. pneumoniae* car-

Oral Tebipenem Pivoxil Hydrobromide in Complicated Urinary Tract Infection

Eckburg et al. NEJM 2022

- **A phase 3 RCT: oral tebipenem pivoxil hydrobromide non-inferior to intravenous ertapenem for complicated urinary tract infection or acute pyelonephritis.**
- **Intervention:** 1372 hospitalized adults
  - oral tebipenem pivoxil hydrobromide (two 300-mg tablets every 8 hours) plus dummy ertapenem infusion every 24 hours
  - intravenous ertapenem (1 g every 24 hours) plus dummy tebipenem pivoxil hydrobromide
- The primary efficacy end point — overall response (clinical cure plus microbiologic response) at the test-of-cure visit was assessed among 868 patients with confirmed complicated urinary tract infection or acute pyelonephritis.
- Overall response at the end-of-treatment visit was 97.3% in the tebipenem pivoxil hydrobromide group and 94.5% in the ertapenem group



Sulopenem for the Treatment of Complicated Urinary Tract Infections Including Pyelonephritis: A Phase 3, Randomized Trial

Dunne et al Clin Inf Dis 2023

- 1392 patients enrolled with cUTI
- 444 sulopenem IV then os Vs 440 ertapenem 5 days IV followed by oral ciprofloxacin or amoxicillin-clavulanate
- Baseline ESBL 26.6%, FQ R 38.6%
- The primary end point was overall combined clinical and microbiologic response at the test-of-cure visit (day 21):
  - **noninferiority of sulopenem was not demonstrated, 67.8% vs 73.9% (95%IC−12.0 to −.1%).**
- Microbiologic success rates were lower in the sulopenem group (71.2% Vs. 78%)
- Clinical success rates were high and similar in both treatment groups at TOC (89.4% Vs. 88.4%)
- The difference was driven by a lower rate of asymptomatic bacteriuria in the subgroup of ertapenem-treated patients who stepped down to ciprofloxacin.

RESEARCH Open Access

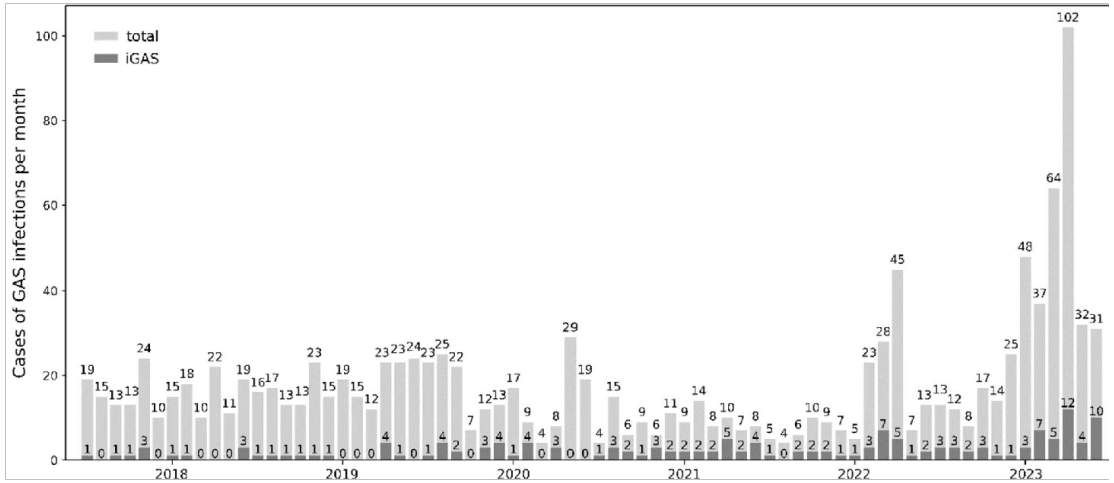
Invasive group A streptococcal infections requiring admission to ICU: a nationwide, multicenter, retrospective study (ISTRE study)

Critical Care

- **Background** Group A *Streptococcus* is responsible for severe and potentially lethal invasive conditions requiring intensive care unit (ICU) admission, such as streptococcal toxic shock-like syndrome (STSS). A rebound of invasive group A streptococcal (iGAS) infection after COVID-19-associated barrier measures has been observed in children. Several intensivists of French adult ICUs have reported similar bedside impressions without objective data.
- **Aim** We aimed to compare the incidence of iGAS infection before and after the COVID-19 pandemic, describe iGAS patients' characteristics, and determine ICU mortality associated factors.
- **Methods** We performed a retrospective multicenter cohort study in **37 French ICUs**, including all patients admitted for iGAS infections for two periods: two years before period (October 2018 to March 2019 and October 2019 to March 2020) and a one-year after period (October 2022 to March 2023) COVID-19 pandemic. iGAS infection was defined by Group A Streptococcus isolation from a normally sterile site. iGAS infections were identified using the International Classification of Diseases and confirmed with each center's microbiology laboratory databases. The incidence of iGAS infections was expressed in case rate.
- **Results** **222 patients** were admitted to ICU for iGAS infections: 73 before and 149 after COVID-19 pandemic. Their case rate during the period before and after COVID-19 pandemic was **205 and 949/100,000 ICU admissions, respectively ($p < 0.001$), with more frequent STSS after the COVID-19 pandemic (61% vs. 45%, $p = 0.015$)**. iGAS patients (n = 222) had a median SOFA score of 8 (5–13), invasive mechanical ventilation and norepinephrine in 61% and 74% of patients. ICU mortality in iGAS patients was 19% (14% before and 22% after COVID-19 pandemic; $p = 0.135$).

Orieux et al. Critical Care (20249

- Increase in invasive group A streptococcal infections in Milan, Italy: a genomic and clinical characterization (Mangioni et al Frontiers 2024)
- Epidemiological changes in invasive Streptococcus pyogenes infection during the UK alert period: A molecular comparative analysis from a tertiary Spanish hospital in 2023 (Barrueco et al Enferm Clin 2024)
- Population of invasive group A streptococci isolates from a German tertiary care center is dominated by the hypertoxigenic virulent M1UK genotype (Walters et al Infection 2023)



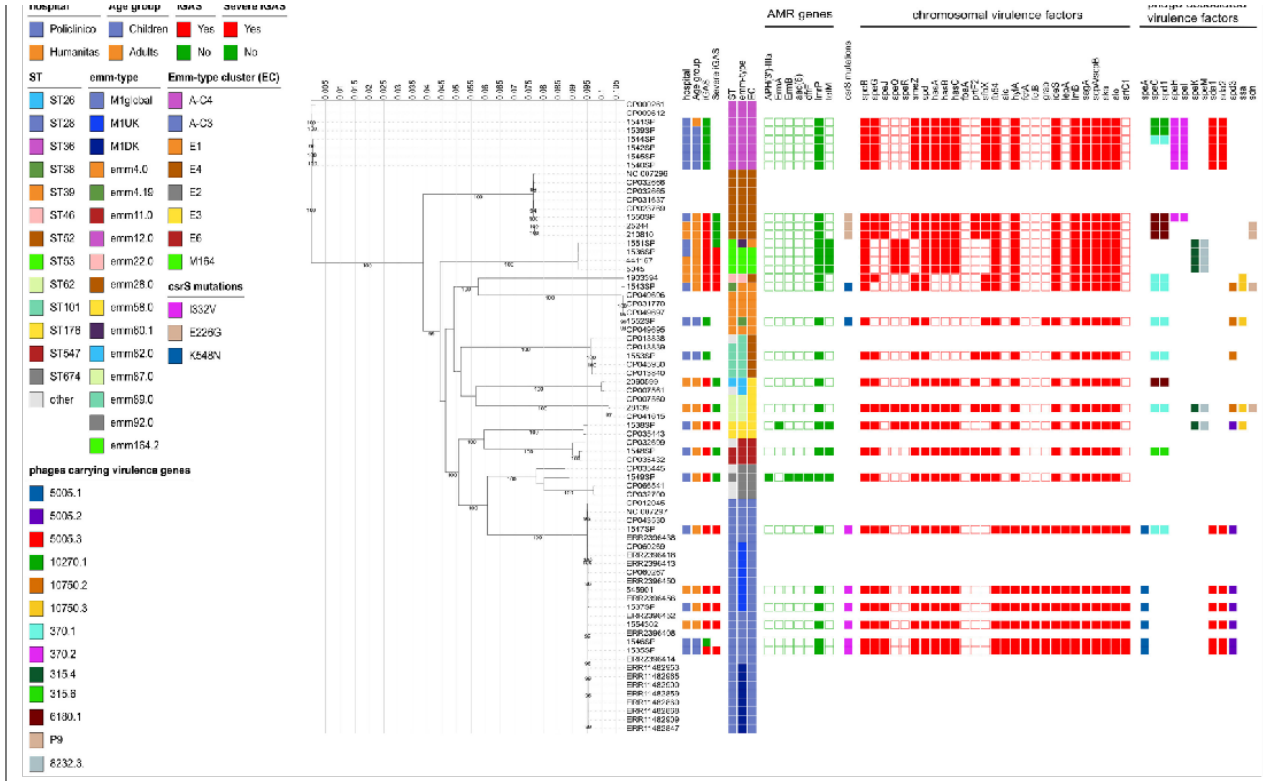


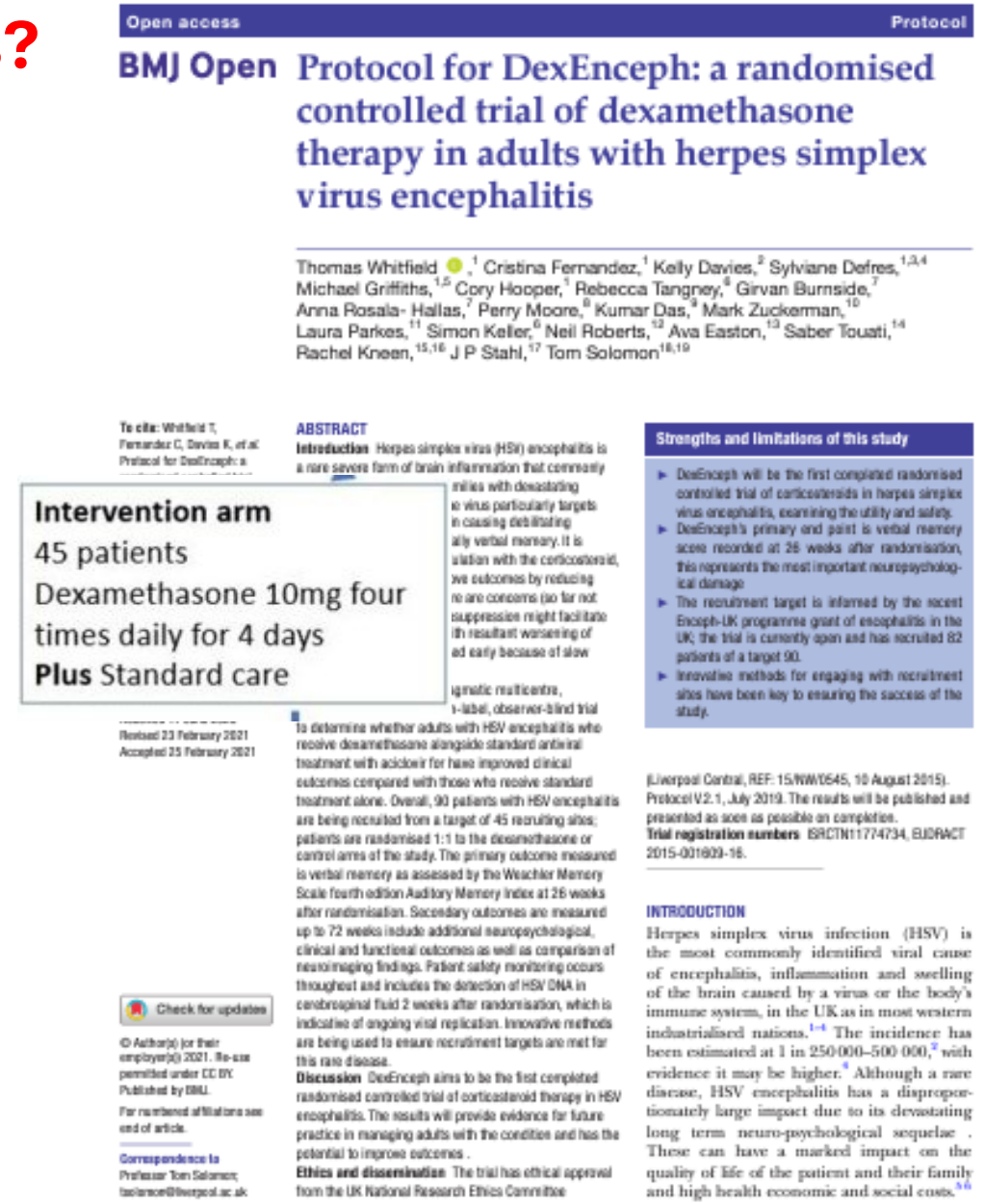
FIGURE 2
Estimated maximum likelihood phylogenetic analysis of Streptococcus pyogenes isolates (n = 28) and reference genomes (n = 45). The phylogeny was estimated on a coreSNP of 12,596 bp with IqTree using the best-fit model of nucleotide substitution TVM + F + ASC + R2 with 1,000 replicates fast bootstrapping. Leaves number represent the sample IDs, bootstraps values higher than 90 are shown on branches. Information regarding the samples were reported: hospital, age group, presence of invasive GAS infection (iGAS), presence of severe iGAS, Sequence Type (ST), *emm*-type, *emm*-type cluster (EC), the presence (filled squared) or absence of antimicrobial resistance genes, *csr*S mutations identified, presence (filled square) or absence of virulence factors, divided in chromosomal (red) or phage-associated (color based on phage on which they are present).

What about Steroids in HSV Encephalitis? DexEnceph trial

Multicentre**, randomised, controlled, open-label, observer-blind trial** to determine whether adults with HSV encephalitis **who receive dexamethasone alongside standard antiviral treatment with aciclovir for have improved clinical outcomes compared** with those who receive standard treatment alone.
Patients: overall**, 90 patients randomised 1:1 to the dexamethasone** or control arms of the study.

Outcomes:

- **primary outcome: verbal memory as assessed by the Weschler Memory Scale** fourth edition **Auditory Memory Index at 26 weeks after randomisation**.
- Secondary outcomes are measured up to 72 weeks include additional neuropsychological, clinical and functional outcomes as well as comparison of neuroimaging findings. Patient safety monitoring occurs throughout and includes the detection of HSV DNA in cerebrospinal fluid 2 weeks after randomisation, which is indicative of ongoing viral replication.



Open access Protocol

BMJ Open

Protocol for DexEnceph: a randomised controlled trial of dexamethasone therapy in adults with herpes simplex virus encephalitis

Thomas Whitfield, Cristina Fernandez, Kelly Davies, Sylviane Defres, Michael Griffiths, Cory Hooper, Rebecca Tangney, Girvan Burnside, Anna Rosala-Hallas, Perry Moore, Kumar Das, Mark Zuckerman, Laura Parkes, Simon Keller, Neil Roberts, Ava Easton, Saber Touati, Rachel Kneen, J P Stahl, Tom Solomon

ABSTRACT

Introduction Herpes simplex virus (HSV) encephalitis is a rare severe form of brain inflammation that commonly

Intervention arm
45 patients
Dexamethasone 10mg four times daily for 4 days
Plus Standard care

to determine whether adults with HSV encephalitis who receive dexamethasone alongside standard antiviral treatment with aciclovir for have improved clinical outcomes compared with those who receive standard treatment alone. Overall, 90 patients with HSV encephalitis are being recruited from a target of 45 recruiting sites; patients are randomised 1:1 to the dexamethasone or control arms of the study. The primary outcome measured is verbal memory as assessed by the Weschler Memory Scale fourth edition Auditory Memory Index at 26 weeks after randomisation. Secondary outcomes are measured up to 72 weeks include additional neuropsychological, clinical and functional outcomes as well as comparison of neuroimaging findings. Patient safety monitoring occurs throughout and includes the detection of HSV DNA in cerebrospinal fluid 2 weeks after randomisation, which is indicative of ongoing viral replication. Innovative methods are being used to ensure recruitment targets are met for this rare disease.

Discussion DexEnceph aims to be the first completed randomised controlled trial of corticosteroid therapy in HSV encephalitis. The results will provide evidence for future practice in managing adults with the condition and has the potential to improve outcomes.

Ethics and dissemination The trial has ethical approval from the UK National Research Ethics Committee

Strengths and limitations of this study

- DexEnceph will be the first completed randomised controlled trial of corticosteroids in herpes simplex virus encephalitis, examining the utility and safety.
- DexEnceph's primary end point is verbal memory score recorded at 26 weeks after randomisation, this represents the most important neuropsychological damage
- The recruitment target is informed by the recent Enceph-UK programme grant of encephalitis in the UK; the trial is currently open and has recruited 82 patients of a target 90.
- Innovative methods for engaging with recruitment sites have been key to ensuring the success of the study.

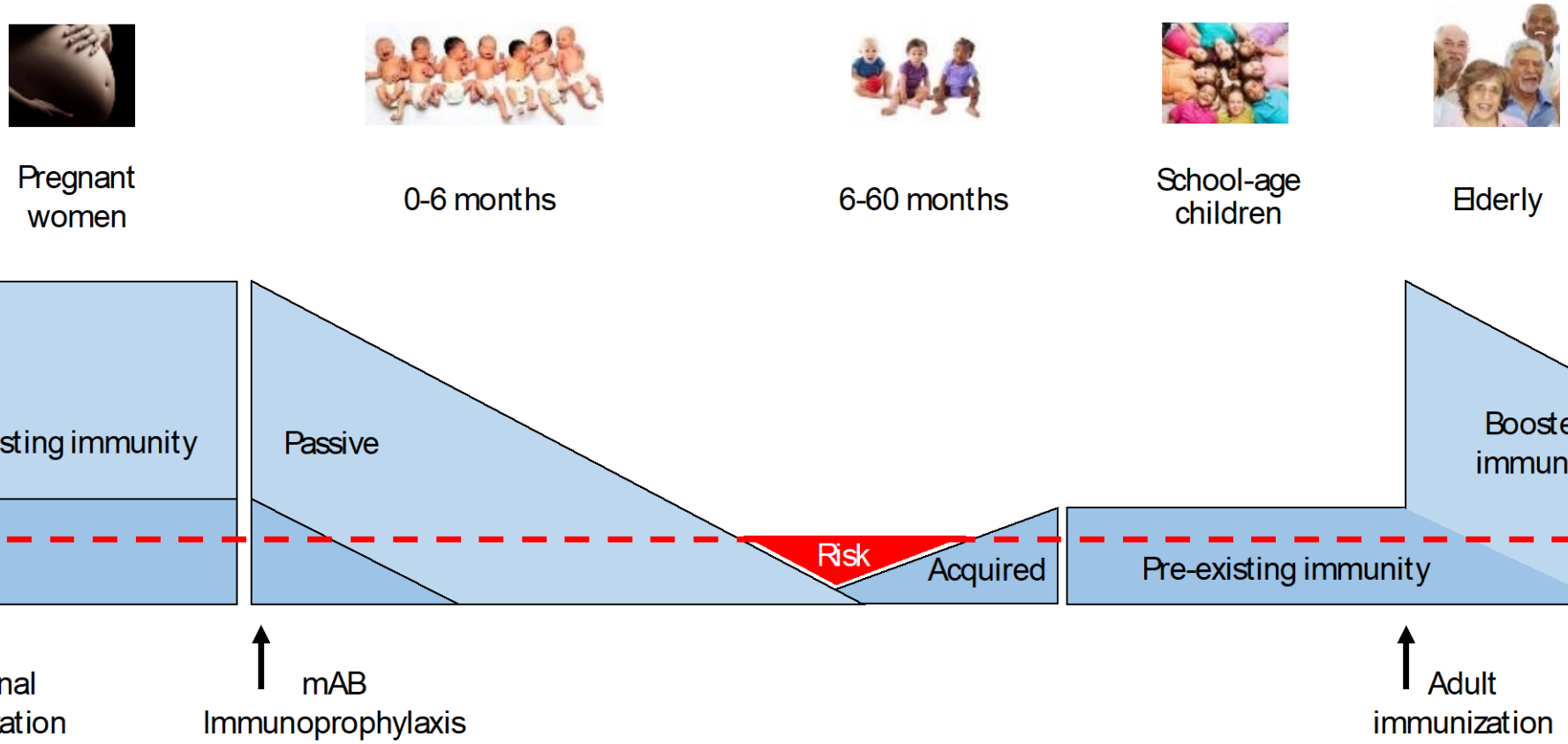
(Liverpool Central, REF: 15/NW/0545, 10 August 2015). Protocol V2.1, July 2019. The results will be published and presented as soon as possible on completion.

Trial registration numbers ISRCTN11774734, EUDRACT 2015-001809-16.

INTRODUCTION

Herpes simplex virus infection (HSV) is the most commonly identified viral cause of encephalitis, inflammation and swelling of the brain caused by a virus or the body's immune system, in the UK as in most western industrialised nations. The incidence has been estimated at 1 in 250 000–500 000, with evidence it may be higher. Although a rare disease, HSV encephalitis has a disproportionately large impact due to its devastating long term neuro-psychological sequelae . These can have a marked impact on the quality of life of the patient and their family and high health economic and social costs.

RSV Prevention



RSV Prevention

ID week 2024; https://www.ema.europa.eu/en/medicines/human/EPAR/mresvia

Nirsevimab

- protects infants from RSV (infants <24 months)
- Monoclonal preF antibody

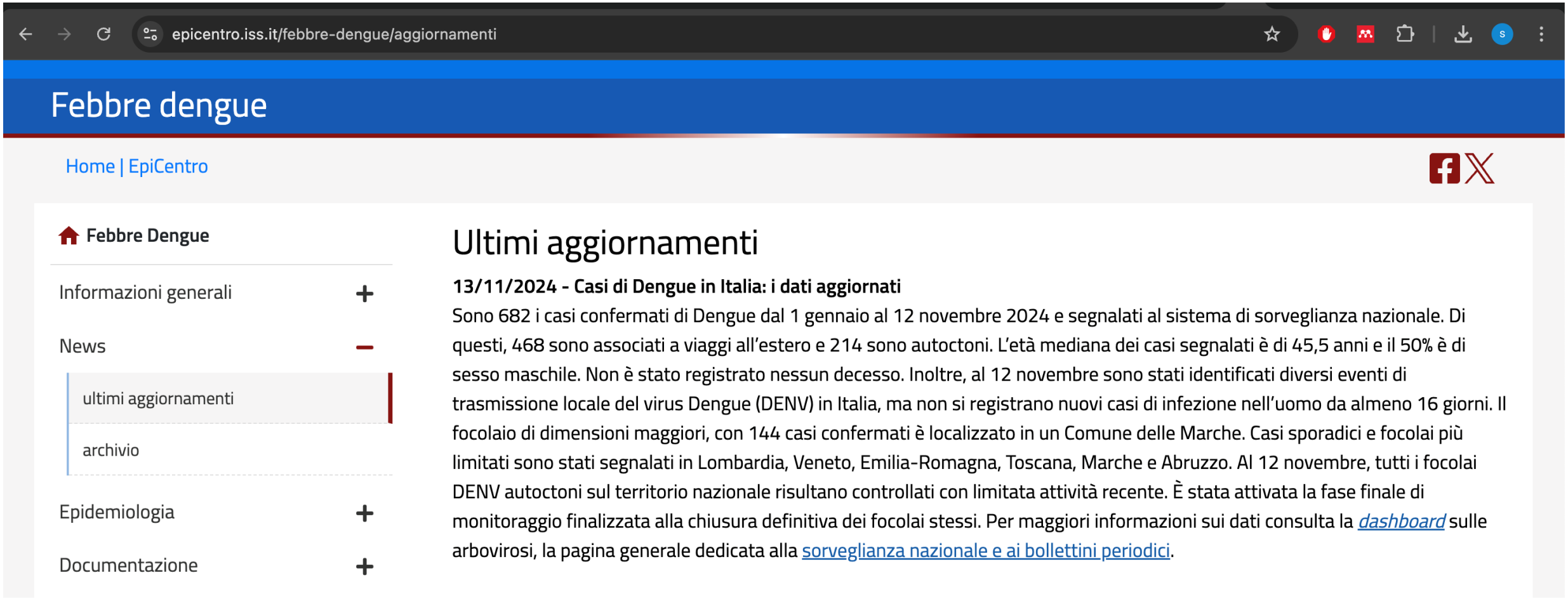
RSVpreF- RSVpreF3

- GSK (RSVPreF3, Arexvy®): RSV A with AS01E adjuvant (RSVA+AS01)
- Pfizer (RSVpreF, Abrysvo ®)contains both RSV A and B, but is unadjuvanted (RSVA/B)→pregnancy
- adults aged 60 years and older

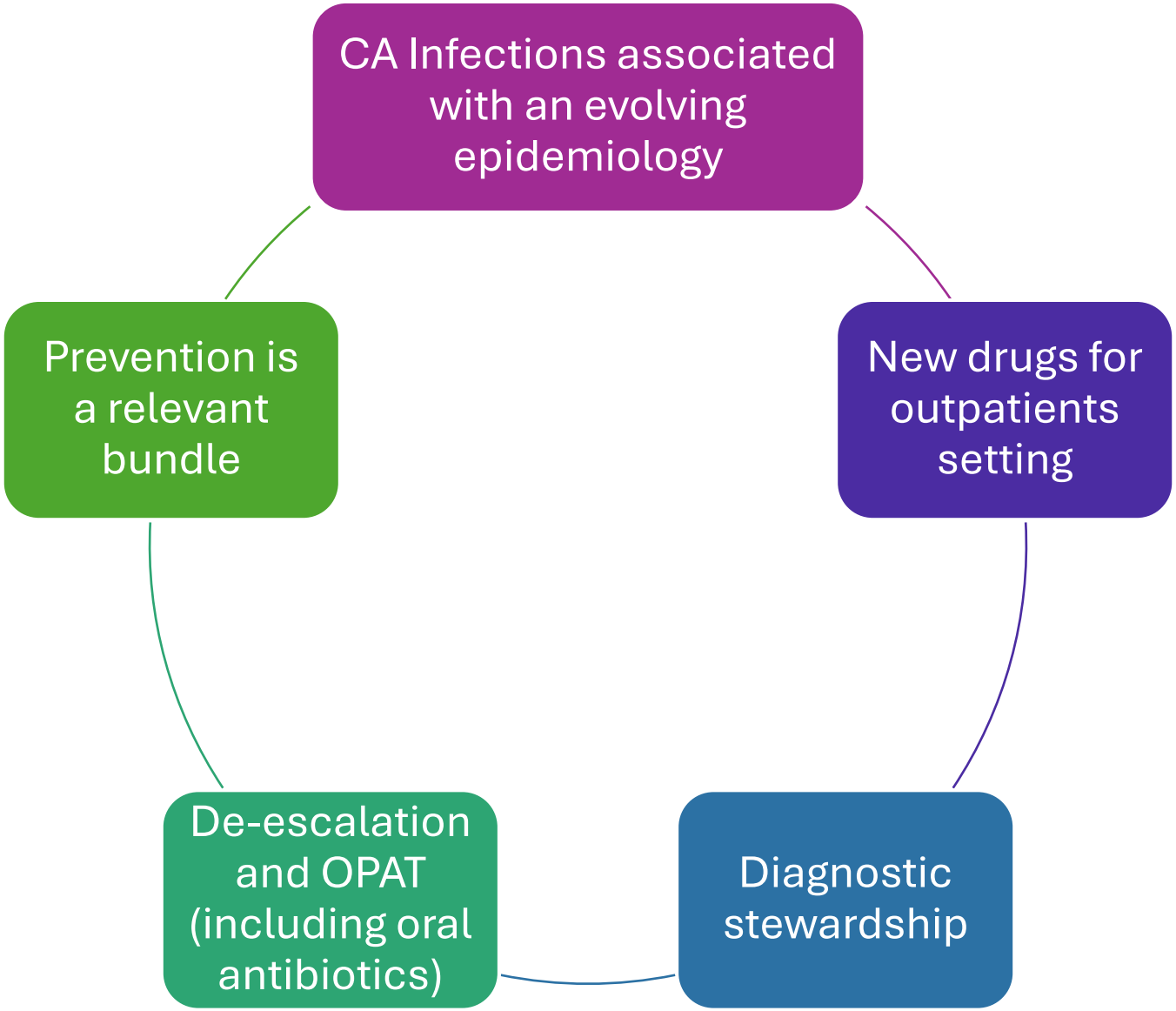
mResVIA

- adults aged 60 years and older
- EMA approval 2024
- 84% reduction in the risk of getting lower respiratory tract disease caused by RSV

Changing Epidemiology & Prevention



Conclusion


CA Infections associated with an evolving epidemiology
New drugs for outpatients setting
Diagnostic stewardship
De-escalation and OPAT (including oral antibiotics)
Prevention is a relevant bundle