New Antibiotic Course Lengths: implications for the medicines supply chain and the new AMR NAP

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On behalf of Danny Palmer (NHS SW Procurement Lead) & Sarah Newsome (NHSE NW AMR Project Lead)

NHS England

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Conflicts of interest

- No financial declarations

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Slido question 1. Are you aware of a push to shorter antibiotic course length?

1. Never heard of it

2. On my radar

3. It's a priority for my work

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5 regions

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UK AMR National Action Plans

Prescribing achievements of 2019-2024	2024-2029 builds on achievements and lessons learned, so by 2029
1. Reducing **human exposure** to antimicrobials by more than **9% since 2014** in challenging circumstances. 2. **Antibiotic course length in primary care** is trending down (4% lower than pre-pandemic) (Dec-19 vs Dec-23) 3. **IV to Oral Switch 2023/24 CQUIN** (on 1st six month's data) shows overall reduction of 7.7%	1. prevent any increase in a specified set **of drug-resistant infections** in humans from the FY 2019-20 baseline 2. prevent any increase in **Gram-negative bloodstream infections** in humans from FY2019-20 3. **Reduce total antibiotic use** in human populations by 5% from the 2019 baseline 4. **Achieve 70%** of total use of antibiotics from the **Access category** (new UK category) across the human healthcare system 5. Increase UK public and healthcare professionals' **knowledge on AMR by 10%,** using 2018 and 2019 baselines, respectively

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Strategic Aims – Antimicrobial Prescribing & Medicines Optimisation (APMO): to improve patient outcomes, safely reduce human exposure to antimicrobials, reduce antimicrobial resistance and reduce environmental impact and waste

NHS England

1. Reduce demand	Reduce clinical need by prevention Reduce patient expectation	e.g. with vaccination, public health, IPC, patient empowerment
2. Reduce exposure	Safely reduce overprescribing Shortest effective course length Narrowest effective spectrum	e.g. with patient risk assessment and decision aids including diagnostic tests
3. Optimise infection management	Investigation, diagnosis & source control Immediate or deferred treatment Effective drug choice, route, dose Timely review & revise prescription	e.g. with evidence-based guidelines supported by digital and medical technology, ensuring equitable access and care

6 | APMO Strategic Aims

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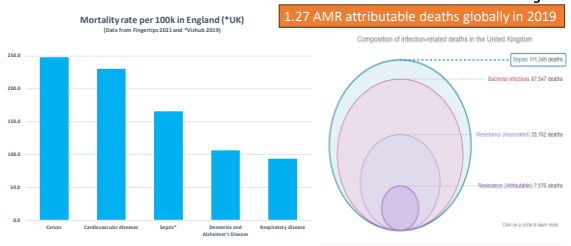
Bacterial infections are 3rd biggest killer in UK

NHS England

1.27 AMR attributable deaths globally in 2019



https://fingertips.phe.org.uk/profile/mortality-profile https://vizhub.healthdata.org/microbe/

Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet. 2022 Feb 12;399(10325):629-655

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Power of Antibiotics (courtesy of Brad Spellberg #shorterisbetter)

Disease	Pre-Antibiotic Death Rate	Death With Antibiotics	Change in Death (ARR)
Community Pneumonia[1]	~35%	~10%	**-25%**
Hospital Pneumonia[2]	~60%	~30%	**-30%**
Heart Infection[3]	~100%	~25%	**-75%**
GNB Bacteremia[4]	~80%	~10%	**-70%**
Brain Infection[5]	>80%	<20%	**-60%**
Skin Infection[6]	11%	<0.5%	**-10%**
By comparison…treatment of myocardial infarction with aspirin or fibrinolytic drugs[7]			**-3%**

[1]IDSA Position Paper '08 Clin Infect Dis 47(S3):S249-65; [2]IDSA/ACCP/ATS/SCCM Position Paper '10 Clin Infect Dis 51(S1):S150-70; [3]Kerr AI. Subacute Bacterial Endocarditis. Springfield IL: Charles C. Thomas, 1955 & Lancet 1935 226:383-4; [4]Spittel '54 Staff Proc Mayo Clin; Spittel '56 Ann Int Med 44:302-315; Hall & Gold '55 Arch Int Med 96:403-12; [5]Lancet '38 231:733-4 & Waring et al. '48 Am J Med 5:402-18; [6]Spellberg et al. '09 Clin Infect Dis 49:383-91 & Madsen '73 Infection 1:76-81; [7] '88 Lancet 2:349-60

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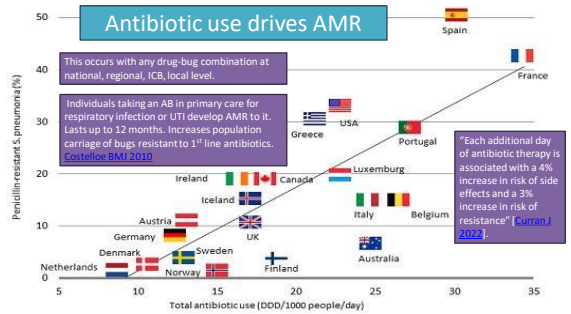
Antibiotic use drives AMR



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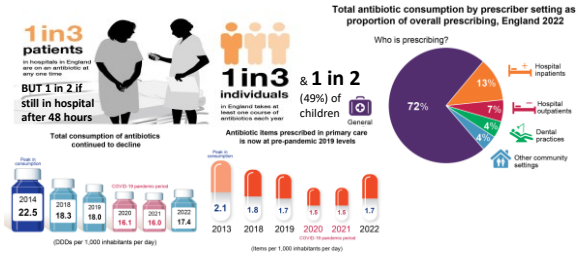

- GPs, minor injuries (ED), walk-in centres, OOH services, Dentists: best guess treatment & occasionally may adjust treatment if not improving or samples sent.
- Hospital in-patients: start best guess, then adjust based on pathology results

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Inappropriate antibiotic prescribing defined

Estimated that 20% of antibiotic prescribing in community[1] & hospitals[2] is inappropriate (excess days), so 10% reduction expected.

1. Smieszek 2018 JAC;
2. Hood 2018 ECCMID poster

Prescribing an antibiotic for a patient in the absence of (documented) evidence of bacterial infection. ***"Just in case"***

Prescribing a **critical broad-spectrum antibiotic** (*piperacillin-tazobactam or carbapenems in secondary care; co-amoxiclav, cephalosporins and fluoroquinolones in primary care)* to patients in the absence of (documented) rationale.

Continuing an antibiotic prescription beyond the course length recommended in local or national guidelines, in the absence of a (documented) rationale.

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Antimicrobial Stewardship is improving outcomes for patients with infections without causing harm or increasing AMR

Schuts meta-analysis: strong evidence[1]
- ↓ mortality
  - empiric guideline adherence (35%↓ RRR)
  - de-escalation based on C&S (66%↓ RRR)
- IV to oral switch = ↓Length of stay + ↓£££, ↑cure

Taconelli (Baur) – meta-analysis of AMS on AMR
- ↓AMR Gram +ve by 43% (MRSA by 49%)
- ↓AMR Gram -ve by 28% (Carbapenem-resistant Enterobacterales by 48%)
- ↓ C difficile infections by 32%

Schuts EC, et al. Lancet Infect Dis 2016; 16(7): 847-56.
Baur, Lancet Infect Dis 2017 17(9): 990-1001

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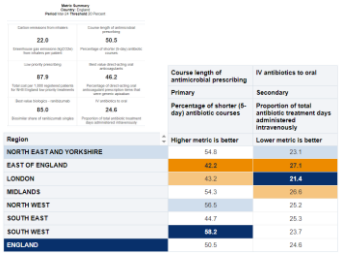
NHSE Medicines Optimisation Opportunities

ICBs were requested to prioritise 5 of 16 medicines optimisation opportunities.

Antibiotic opportunities
- Reducing course length of antimicrobial prescribing courses
- Switching IV antibiotics to oral

National MO Opportunities dashboard to report performance at all levels on ePACT2



Region	Course length of antimicrobial prescribing: Primary: Percentage of shorter (5-day) antibiotic courses	IV antibiotics to oral: Secondary: Proportion of total antibiotic treatment days administered intravenously
	Higher metric is better	Lower metric is better
NORTH EAST AND YORKSHIRE	54.8	23.1
EAST OF ENGLAND	42.2	27.1
LONDON	43.2	21.4
MIDLANDS	54.3	26.6
NORTH WEST	56.5	25.2
SOUTH EAST	44.7	25.3
SOUTH WEST	59.2	23.7
ENGLAND	50.5	24.6

https://www.england.nhs.uk/long-read/national-medicines-optimisation-opportunities-2023-24/ 13

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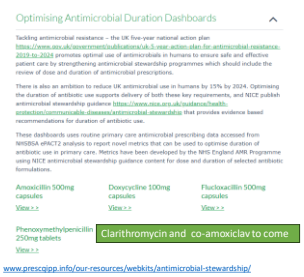
Resources to support shorter durations



www.prescqipp.info/our-resources/webkits/antimicrobial-stewardship/

https://future.nhs.uk/A_M_R/view?objectId=39575888

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Infographics to support 5-day Rx

Used as practice screensavers or posters.

1. Visual timeline to depict course lengths for common infections for adults. In line with NICE guidance for first line treatments only.
2. Aims to promote the 5-day course length for common infections in adults.
3. Safety messaging of avoiding prolonged durations of antibiotic therapy.

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Why do we need antibiotics in the correct pack sizes?

Community pharmacy dispense the quantity on the prescription.
- Cutting off excess tablets is an inefficiency!
- Pharmacy First Scheme PGDs:
  - **UTIs** –3 days nitrofurantoin (6 x m/r 100mg BD or 12 x 50mg QDS)
  - **Impetigo / insect bites** – 5 days of flucloxacillin QDS or clarithromycin BD or erythromycin QDS
  - **Sore throat** – 5 days of penicillin V QDS or clarithromycin or erythromycin
  - **Rhinosinusitis** – 5 days clarithromycin or doxycycline 200mg LD then 100mg od 4 days (6)
  - **Acute otitis media** – 5 days of amoxicillin TDS or clarithromycin or erythromycin
  - **Shingles** – 7 days of aciclovir 800mg 5x daily (35x800mg or 70x400mg or 140x200mg) or valaciclovir 1g TDS

Hospitals, urgent treatment centres, etc
- Often use existing pack sizes and instruct patients to return excess for destruction by pharmacy (part of NHS contract)
- Leftovers: returned, kept for next time, shared with friends / family, put in dustbin, flushed down the toilet. Environmental contamination with antibiotics needs to be avoided.

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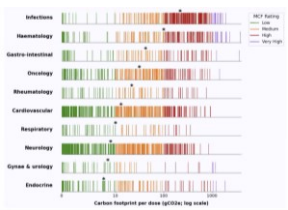
A landscape analysis of medicine carbon footprints identifies antibiotics as promising targets for emission reduction interventions



Each line = single product,
Asterisk = median gCO2 per dose

https://formulary.mcf-classifier.com/

https://papers.ssrn.com/sol3/papers.cfm?abstract_id=4633938

2.2 billion prescribed doses of medicines in England in Jan 2023
- total footprint of 140,000 tonnes CO2e
- = monthly emissions of 940,000 cars
- 3 antibiotics: amoxicillin, flucloxacillin, and penicillin V contributed 15% of emissions.

Implementing the recommended 20% antibiotic prescription reduction could save:
- 4,200 tonnes CO2e / month
- = to removing 29,000 cars

ICS Sustainability Checklist www.pharmacydeclares.co.uk for pharmacy services' green plans includes a section on AMS with shorter courses as a goal

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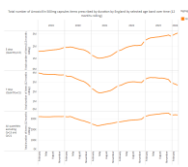
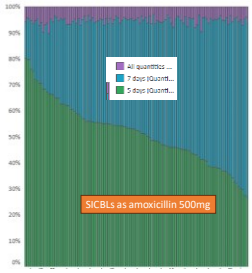
Amoxicillin: NICE all 5-days except 5-7d for AOM & 7d for non-CF bronchiectasis & only if susceptible CAUTI & lower UTI

- Pack sizes of 15 or 21
- Liquid: 5ml TDS 7d = 105ml = 2 bottles as community pharmacy must dispense qty on Rx
- Tariff 500mg 15 = 108p, 21 = 151p. 43p saving or £1.3m per month
- Devon ↑28% (SystmOne formulary to 5d & Scriptswitch prompt)





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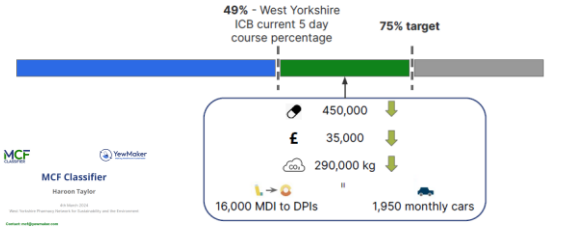
Practical applications - antimicrobial stewardship

NHS England National Medicines Optimisation Opportunities for 2023/24 recommended that 75% of amoxicillin prescriptions should be 5-day courses by March 2024.



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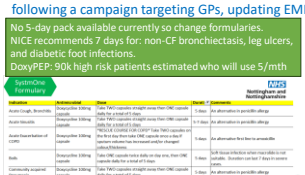
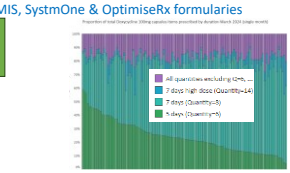
Doxycycline: Nottingham & Notts NHS are at 56% (vs 15% South Yorkshire ICB) for 5-day Rx following a campaign targeting GPs, updating EMIS, SystmOne & OptimiseRx formularies

No 5-day pack available currently so change formularies.
NICE recommends 7 days for: non-CF bronchiectasis, leg ulcers, and diabetic foot infections.
DoxyPEP: 90k high risk patients estimated who will use 5/mth





Shorter is Better – Doxycycline (PRESCqipp AMS VPG webinar)
by Deepa Baxi – Senior Medicines Optimisation Pharmacist

https://www.prescqipp.info/our-resources/webkits/antimicrobial-stewardship/optimising-antimicrobial-duration-dashboard-doxycycline-100mg-capsules/

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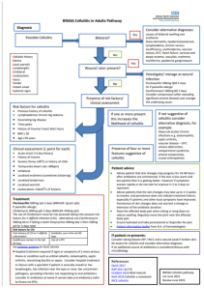
Flucloxacillin: NICE only recommends 7 days for leg ulcers and diabetic foot infection

- No 5-day pack so formulary change
- Cellulitis is 5-7 days (but 5d based on levofloxacin evidence)
  - USA recommends 5-days (as effective as 10-day course) for uncomplicated cellulitis (IDSA) since 2014 *"The recommended duration of antimicrobial therapy is 5 days, but treatment should be extended if the infection has not improved within this time period (strong, high)."*
- BNS&SG ICB switched in Jun-21 and saw no increase in hospital admissions when audited for 12 months to Apr-23 View Inpatient admissions - Antimicrobial Resistance - Model Health System
- PRESCQIPP AMS VPG Webinar by Liz Jones



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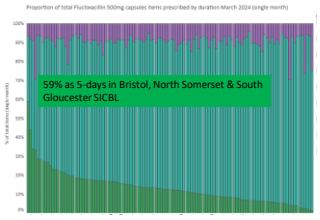
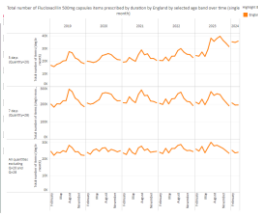
Flucloxacillin: NICE only recommends 7 days for leg ulcers and diabetic foot infection





Use of shorter 5-day packs continues to grow

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Penicillin: NICE does not recommend 7 days alone in any guideline

- Acute sore throat: 5 to 10 days.
  - 5-days enough for symptomatic cure
  - 10 days to increase chance of microbiological cure (in proven GAS).

Advise paracetamol, or if preferred and suitable, ibuprofen for pain.
Medicated lozenges may help pain in adults.
Use FeverPAIN or Centor to assess symptoms:
FeverPAIN 0-1 or Centor 0-2: no antibiotic;
FeverPAIN 2-3: no or back-up antibiotic;
FeverPAIN 4-5 or Centor 3-4: immediate or back-up antibiotic.
Systemically very unwell or high risk of complications: immediate antibiotic.

FeverPAIN criteria: score 1 point for each (max score of 5).
- **Fever** (during previous 24 hours).
- **P**urulence (pharyngeal/tonsillar exudate).
- **A**ttend rapidly (within 3 days after onset of symptoms).
- **I**nflamed tonsils.
- **N** cough or coryza.

• score of 0 or 1 = 13-18% likelihood of isolating streptococcus.
• score of 2 or 3 = 34-40% likelihood of isolating streptococcus.
• score of 4 or 5 = 62-65% likelihood of isolating streptococcus.

Centor criteria: score 1 point for each (maximum score of 4).
- Tonsillar exudate.
- Tender anterior cervical lymphadenopathy or lymphadenitis.
- History of fever (over 38°C).
- Absence of cough.

• score of 0, 1 or 2 = 3-17% likelihood of isolating streptococcus.
• score of 3 or 4 = 32-56% likelihood of isolating streptococcus.

Sinusitis is 5-days

In NHS Wales during iGAS outbreak, only 31% who scored 2+ FEVERpain had a +ve GAS RADT (in print). Only 10% referred from community pharmacy to GP or ED

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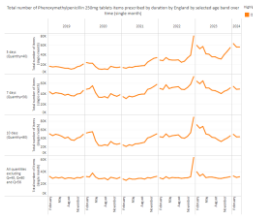
Penicillin: NICE does not recommend 7 days alone in any guideline



Sore throat: 5-10 days & sinusitis is 5-days

Hospitals issue xx pre-packs per annum

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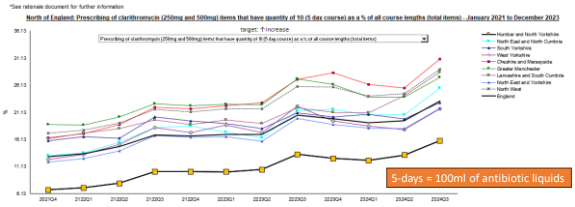
Clarithromycin: only 7 days recommended for non-CF bronchiectasis, leg ulcer or diabetic foot. Rest 5 days or 5-7days



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Penicillin allergy label & delabeling

- 5.9% have a PenA label. 10-20% of hospital admissions.
- >90% are inaccurate labels when tested
- 6 extra deaths per 1000 patients in next year
- 8% higher mortality in pneumonia.
- 4.7x more likely to receive Watch or Reserve antibiotic
- 27% more *C.difficile* infection
- Framework for PenA delabelling by non-specialists in UK.
  - NENC ICB have guideline for ICB in hospital
- 9% of PenA patients in primary care have had a penicillin since label.
  - 50-90% can be delabeled from history alone (North Tyneside / draft in NENC ICB)
- Resources in Future NHS AMR workspace to support implementation
- 27th Sept: launch PADL initiative to start delabeling inappropriate patients, so possibly a decrease in clarithromycin use over time

West JAC 2019 https://doi.org/10.1093/jac/dkz127 Powell JHI 2019 https://doi.org/10.1016/j.jhin.2018.11.020
Powell JHI 2019 https://doi.org/10.1016/j.jhin.2021.04.011

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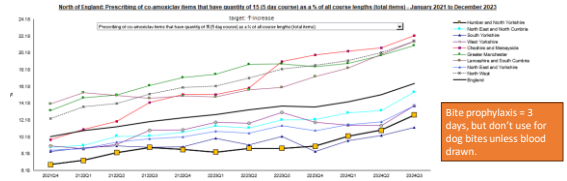
CoAmoxiclav: 7d for non-CF bronchiectasis, leg ulcer, cellulitis near eyes/nose, & **only if C&S sensitive** pyelonephritis or CAUTI



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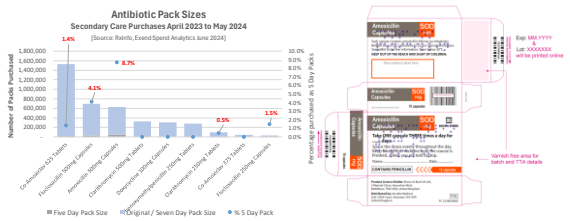
RX-info: over-labelled antibiotics packs purchased in last 12 months to May-24

5-day packs are significantly low and reflect the market conditions. Make them and we will use them!



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What new pack sizes do we need?

Drug, strength, formulation	Pack size
Priority 1 - High	
Nitrofurantoin 100mg m/r cap	6
Doxycycline 100mg capsules	6
Phenoxymethylpenicillin 250mg tablets	20
Flucloxacillin 500mg capsules	20
Clarithromycin 500mg tablets	10
Cefalexin 500mg capsules/tabs	15
Flucloxacillin 250mg capsules	20
Co-amoxiclav 500mg/125mg tablets	9
Co-amoxiclav 250mg/125mg tablets	15
Drug, strength, formulation	**Pack size**
Priority 2 - Medium	
Metronidazole 400mg tablets	15
Nitrofurantoin 50mg tablets/caps	12
Clarithromycin 250mg tablets	10
Amoxicillin 500mg capsules	9
Cefalexin 500mg capsules	6

Drug, strength, formulation	Pack size required
Priority 3 - Low	
Ciprofloxacin 500mg tablets	14
Amoxicillin 500mg capsules	28
Cefalexin 500mg capsules/ tabs	14
Pivmecillinam 200mg tablets	22
Trimethoprim 200mg tablets	10
Doxycycline 100mg capsules	15
Nitrofurantoin 50mg capsules	28
Metronidazole 200mg tablets	15
Metronidazole 400mg tablets	9
Erythromycin 250mg g/r tablets	20
Doxycycline 100mg capsules	10
Cefalexin 250mg tablets	14
Nitrofurantoin 100mg m/r cap	8
Metronidazole 400mg tablets	10
Metronidazole 400mg tablets	28
Ofloxacin 200mg tablets	28
Amoxicillin 250mg capsules	28
Cefalexin 500mg capsules/ tabs	10
Ciprofloxacin 250mg tablets	14
Ofloxacin 400mg tablets	28

Drug, strength, formulation	Pack size required
Priority 3 - Low	
Co-trimoxazole 160mg/800mg tab	14
Nitrofurantoin 100mg capsules	28
Trimethoprim 100mg tablets	6
Co-trimoxazole 80mg/400mg tablets	14
Azithromycin 500mg tablets	5
Co-trimoxazole 80mg/400mg tablets	6
Ciprofloxacin 750mg tablets	14
Cefalexin 250mg capsules	21
Doxycycline 100mg capsules	4
Azithromycin 500mg tablets	4
Mancomycin 125mg capsules	40
Levofloxacin 500mg tablets	7
Co-trimoxazole 160mg/800mgtab	10
Nitrofurantoin 100mg tablets	12
Doxycycline 100mg disp SF tab	14
Levofloxacin 250mg tablets	14
Erythromycin ethylsuccinate 500mg	20

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Slido question: Are you working on any new pack sizes in our high or medium priority list?

1. Not applicable to my line of work
2. Actively working on these pack sizes
3. Something we have been considering
4. Not even considered it

What new pack sizes do we need?

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Shorter Is Better

Diagnosis	Short (d)	Long (d)	Result	#RCT
CAP	3-5	5-14	Equal	14
Atypical CAP	1	3	Equal	1
Possible PNA in ICU	3	14-21	Equal	1*
VAP	5-8	10-15	Equal	3
Empyema	14-21	21-42	Equal	2
Cystic Fibrosis Exacerbation	10-14	14-21	Equal	1
cUTI/Pyelonephritis	5 or 7	10 or 14	Equal	11**
Intra-abd Infection	4	8-10	Equal	3
Complex Appendicitis	1-2	5-6	Equal	2
GNB Bacteremia	7	14	Equal	3†
Cellulitis/Wound/Abscess	5-6	10	Equal	4‡
Osteomyelitis	42	84	Equal	2
Osteo Removed Implant	28	42	Equal	1
Debrided Diabetic Osteo	10-21	42-90	Equal	2¥
Septic Arthritis	14	28	Equal	1
Bacterial Meningitis (peds)	4-7	7-14	Equal	6
AECB & Sinusitis	<5	>7	Equal	>25
Variceal Bleeding	2-3	5-7	Equal	2
Neutropenic Fever	AFx72h/3 d	+ANC>500/9 d	Equal	2
Post Op Prophylaxis	0-1	1-5	Equal	55¥
Erythema Migrans (Lyme)	7-10	14-20	Equal	3
P. vivax Malaria	7	14	Equal	1
Total: 22 Conditions				>130 RCTs

*Infiltrate on CXR but low CPIS score (≤6), both ventilated & non ventilated, likely CAP, HAP, and VAP combined. **2 RCT included males, the smaller one found lower 10-18 d thgr cure in males with 7 days of therapy but no difference at longer follow-up, larger exclusive male study found no diff in cure, 2 Peds RCTs, 1 short course was superior on recurrence, 1 short course had more UTI failure at day 5-14 but not after day 14. †GNB bacteremia also in LTI/d/4 RCTs; ‡3 RCTs equal, 1 (low dose oral flucox) ¥relapses 2° endpoint; ¥all patients debrided, in 1 study total bone resection (clean margins); ¥Includes meta-analysis of 52 RCTs, refs at https://www.bradspellberg.com/shorter-is-better

Will antibiotic courses get even shorter?

- Possibly, but more likely to see POC diagnostics playing a more central role eg NHS Wales community pharmacy sore throat

Is it worth moving to smaller packs?

- Yes. Contracts! NHS efficiencies. Smaller carbon footprint!

Are they guaranteed to have a long enough product life for the investment?

- Yes. It will take time to move to 75% as 5-days

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Summary

- Antibiotics are life-saving medicines
- Antimicrobial stewardship is getting the best outcome for patients with infection whilst minimising harm or increasing AMR
- Use drives resistance, especially with broad-spectrum antibiotics
- Most patients can be treated with shorter (5 days or less) courses

Smaller appropriate pack sizes are needed to reduce dispensing times, leftovers and the carbon footprint.
Packs with standard administration instructions preferred

Pharma should liaise with their "regional buddy" on how best to take smaller pack sizes forward

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