COVID-19 Stewardship challenges and opportunities

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Antibiotics and COVID-19: experience and advice March 2020

Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wu cohort study

Fei Zhou*, Ting Yu*, Ronghui Du*, Guohui Fan*, Ying Liu*, Zhibo Liu*, Jie Xi
Hui Li, Xudong Wu, Jiuyang Xu, Shengjin Tu, Yi Zhang, Hua Chen, Bin Cao

Summary

Background Since December, 2019, Wuhan, China, has
(COVID-19), caused by the severe acute respiratory syndr
clinical characteristics of patients with COVID-19 have bee
clinical course of illness, including viral shedding, have not

Methods In this retrospective, multicentre cohort study, we in
confirmed COVID-19 from Jinyintan Hospital and Wuhar
discharged or had died by Jan 31, 2020. Demographic, cl
samples for viral RNA detection, were extracted from electr
and non-survivors. We used univariable and multivariable
associated with in-hospital death.

Findings 191 patients (135 from Jinyintan Hospital and 56 f
study, of whom 137 were discharged and 54 died in hospital.
being the most common (58 [30%] patients), followed by
(15 [8%] patients). Multivariable regression showed increas
(odds ratio 1·10, 95% CI 1·03–1·17, per year increase; p=0·00
score (5·65, 2·61–12·23; p<0·0001), and d-dimer greater than
Median duration of viral shedding was 20·0 days (IQR 17·0–
death in non-survivors. The longest observed duration of vira

Interpretation The potential risk factors of older age, high SO
clinicians to identify patients with poor prognosis at an earl
for a strategy of isolation of infected patients and optimal an

Funding Chinese Academy of Medical Sciences Innovation
Distinguished Young Scholars; National Key Research and D
Technology Project; and Major Projects of National Science a

JAMA Insights | CLINICAL UPDATE

Care for Critically Ill Patients With COVID-19

Srinivas Murthy, MD, CM, MHSc; Charles D. Gomersall, MBBS; Robert A. Fowler, MD, CM, MSc

Initial reports suggest that COVID-19 is associated with severe disease that requires intensive care in approximately 5% of proven infections.[1] Given how common the disease is becoming, as in prior major severe acute respiratory infection outbreaks—SARS (severe acute respiratory syndrome), MERS (Middle East respiratory syndrome), avian influenza A(H7N9), and influenza A(H1N1)pdm09—critical care will be an integral component of the global response to this emerging infection.

The rapid increase in the number of cases of COVID-19 in Wuhan, China, in late 2019 highlighted how quickly health systems can be challenged to provide adequate care.[1] Case-fatality proportions were 7-fold higher for patients in Hubei Province compared with those outside of the region, 2.9% vs 0.4%, emphasizing the importance of health system capacity in the care of patients who are critically ill with COVID-19.[1]

This article discusses issues pertaining to regions where critical care units have the capacity to provide mechanical ventilation, acknowledging that this capacity does not exist in many regions and that capacity could be exceeded in many places. This differential ability to manage the disease will likely have a substantial influence on patient outcomes.

Factors Associated With Requiring Intensive Care

Appreciating typical clinical features and disease course are crucial both to prepare for increasing numbers of patients and to determine how

Figure. Summary of Caring for Critically Ill Patients With COVID-19

Caring for critically ill patients with COVID-19 is based on the usual management of viral pneumonia with respiratory failure with additional precautions to reduce risk of transmission.

Usual critical care

Many patients with severe COVID-19 develop acute respiratory distress syndrome (ARDS). Evidence-based guidelines for ARDS in the context of COVID-19 include treatments such as

- Conservative intravenous fluid strategies
- Empirical early antibiotics for possible bacterial pneumonia
- Consideration for early invasive ventilation
- Lung-protective ventilation strategies
- Periodic prone positioning during mechanical ventilation
- Consideration of extracorporeal membrane oxygenation

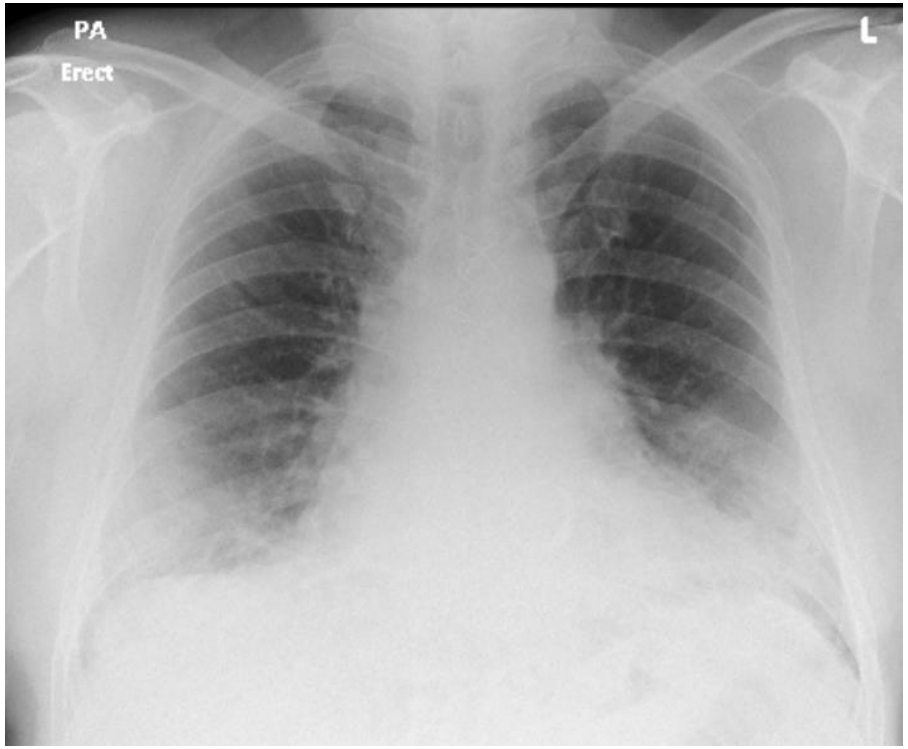
Modifications to usual critical care

- Admission of patients with suspected disease to private rooms when possible
- Use of medical face masks for symptomatic patients during assessment and transfer
- Maintain distancing of at least 2 m between patients
- Caution when using high-flow nasal oxygen or noninvasive ventilation due to risk of dispersion of aerosolized virus in the health care environment with poorly fitting masks
- Clinicians involved with aerosol-generating procedures should use additional airborne precautions including N95 respirators and eye protection

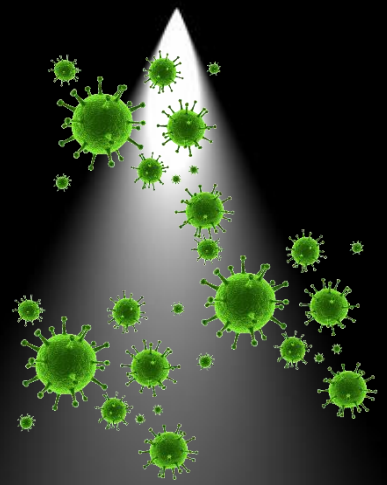
Survivor (n=137)	p value
128 (93%)	0·15
29 (21%)	0·87
31 (23%)	0·0005
10 (7%)	<0·0001
8 (6%)	<0·0001
2 (1%)	<0·0001
1 (1%)	<0·0001
0	0·0054
0	<0·0001

Antibiotics and COVID-19

- **Drivers of antibiotic prescribing**
  - *Diagnostic uncertainty*
    - Bacterial co-infection
    - Bacterial secondary infection
  - *Anti-inflammatory effects of antibiotics?*
  - *Lack of available COVID-19 therapies*
- **Confounders**
  - *Laboratory/sampling – inability to "rule out"*
  - *CRP high and stays high*
- **Unintended consequences of antibiotics**
  - *Antibiotic-related adverse events*
  - *Secondary bacterial and fungal infections*
  - *Antimicrobial Resistance*



COVID-19



Antimicrobial Prescribing

Estimating rates of bacterial co-infection in COVID-19

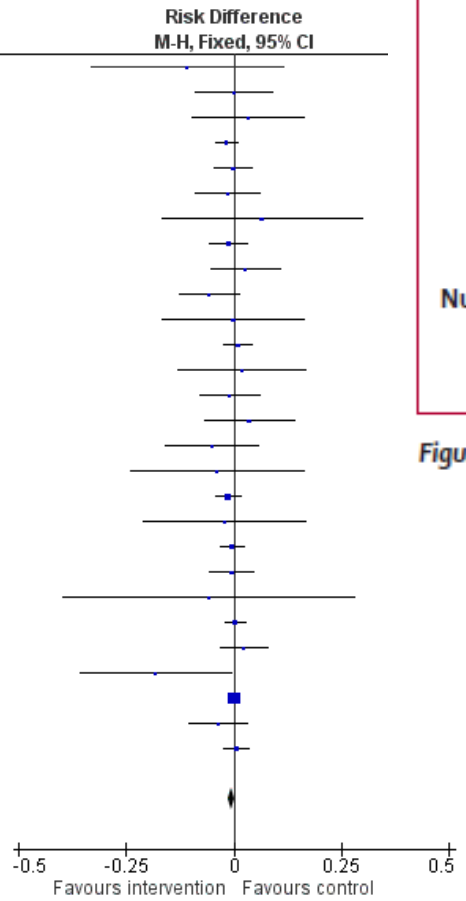
	No. studies	No. pts	When	Co-infection	Secondary infection	Antibiotics
Langford[1]	24	3338	Nov-March	3.5%	14.6%	71.8%
Lansbury[2]	30	3834	Dec-April	4%	14%	>90%
Garcia-Vidal[3]	Single	989	Feb-April	3.1%	4.7%	82% Azith 60.4% Cef
Hughes[4]	Single	836	Feb- April	3.2%	6.1%	Not reported
Karami[5]	Single	925	March- May	1.2% (<1 week)		60.1%

1. Langford et al Clin Micro Infect https://doi.org/10.1016/j.cmi.2020.07.016 2. Lansbury et al J Infection (2020) 81: 266–275 3. Garcia-Vidal et al Clin Micro Infect (2020) https://doi.org/11 4. Hughes et al Clin Micro Infect (2020) 26:1395e1399 5. Karami et al (2020) Infectious Diseases, DOI: 10.1080/23744235.2020.1839672

Clinical outcomes from RCTs of interventions to reduce unnecessary antibiotic use : Mortality, all RCTs

Study or Subgroup	Intervention Events	Intervention Total	Control Events	Control Total	Weight	Risk Difference M-H, Fixed, 95% CI
Annane 2013	7	31	10	30	0.4%	-0.11 [-0.33, 0.12]
Bailey 1997	3	51	3	51	0.6%	0.00 [-0.09, 0.09]
Bouza 2007	92	167	43	83	1.4%	0.03 [-0.10, 0.16]
Camins 2009	11	390	18	394	5.0%	-0.02 [-0.04, 0.01]
Christ-Crain 2004	4	124	4	119	1.5%	-0.00 [-0.05, 0.04]
Christ-Crain 2006	18	151	20	151	1.9%	-0.01 [-0.09, 0.06]
Ding 2013	21	33	20	35	0.4%	0.06 [-0.17, 0.30]
Fine 2003	22	283	29	325	3.8%	-0.01 [-0.06, 0.03]
Fraser 1997	19	141	12	111	1.6%	0.03 [-0.05, 0.11]
Gums 1999	8	127	15	125	1.6%	-0.06 [-0.13, 0.01]
Hochreiter 2009	15	57	14	53	0.7%	-0.00 [-0.17, 0.16]
Kristoffersen 2009	2	103	1	107	1.3%	0.01 [-0.02, 0.04]
Liu 2013	6	42	5	40	0.5%	0.02 [-0.13, 0.17]
Maravic-Stojkovic 2011	7	102	8	103	1.3%	-0.01 [-0.08, 0.06]
Masia 2008	40	140	33	132	1.7%	0.04 [-0.07, 0.14]
Micek 2004	48	150	52	140	1.8%	-0.05 [-0.16, 0.06]
Oliveira 2013	21	49	21	45	0.6%	-0.04 [-0.24, 0.16]
Paul 2006	149	1153	145	1012	13.7%	-0.01 [-0.04, 0.01]
Qu 2012	7	35	8	36	0.5%	-0.02 [-0.21, 0.17]
Schnoor 2010	10	302	13	348	4.1%	-0.00 [-0.03, 0.02]
Schouten 2007	15	207	15	194	2.5%	-0.00 [-0.06, 0.05]
Schroeder 2009	3	14	3	11	0.2%	-0.06 [-0.40, 0.28]
Schuetz 2009	34	671	33	688	8.6%	0.00 [-0.02, 0.03]
Senn 2004	8	126	5	125	1.6%	0.02 [-0.03, 0.08]
Singh 2000	5	39	13	42	0.5%	-0.18 [-0.36, -0.01]
Solomon 2001	60	2624	55	2489	32.4%	0.00 [-0.01, 0.01]
Stolz 2007	5	102	9	106	1.3%	-0.04 [-0.10, 0.03]
Yealy 2005	57	617	61	701	8.3%	0.01 [-0.03, 0.04]
Total (95% CI)		**8031**		**7796**	**100.0%**	**-0.00 [-0.01, 0.00]**
Total events	697		668			

Heterogeneity: Chi² = 16.34, df = 27 (P = 0.95); I² = 0%
Test for overall effect: Z = 1.13 (P = 0.26)



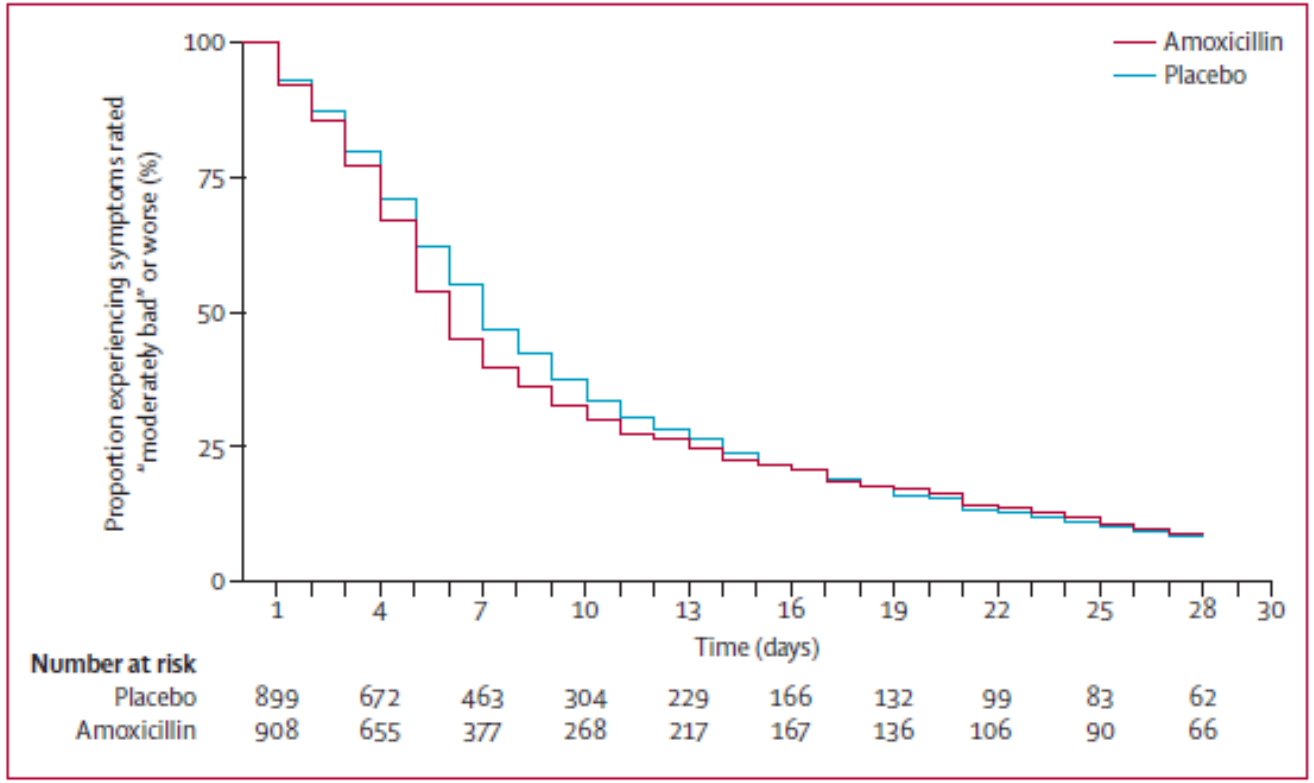


Figure 2: **Kaplan-Meier estimates for duration of symptoms rated "moderately bad" or worse**

P. Little et al Lancet Inf Dis 2013; 13: 123-29

Cochrane Database of Systematic Reviews
9 FEB 2017 DOI: 10.1002/14651858.CD003543.pub4

Azithromycin and Doxycycline

RECOVERY
Randomised Evaluation of COVID-19 Therapy

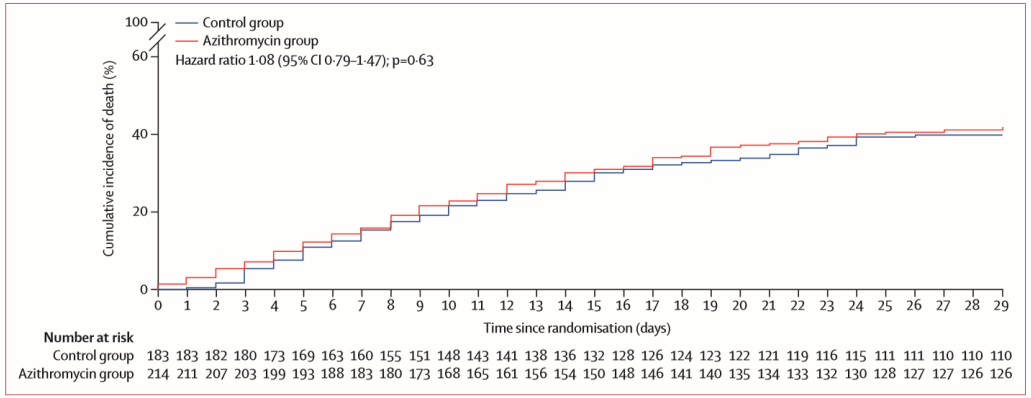
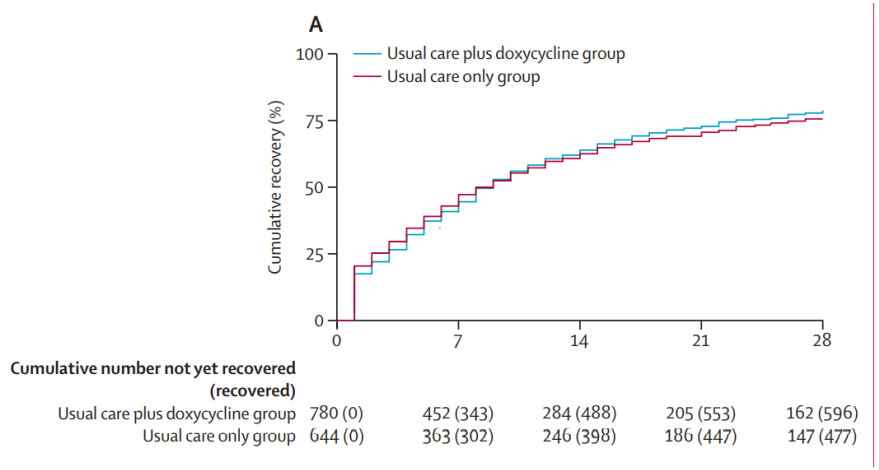
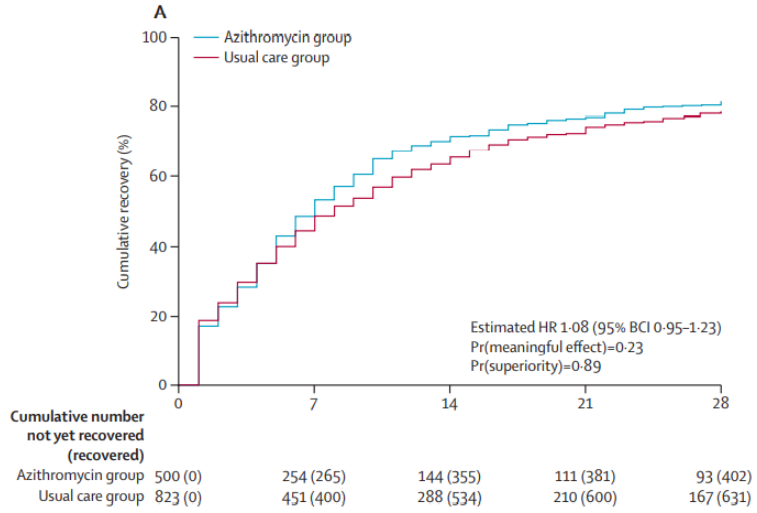


Figure 2: **Cumulative incidence of all-cause mortality at 29 days after randomisation**
Numbers estimated by the Kaplan-Meier method, and hazard ratio with corresponding 95% CI calculated from a Cox proportional hazards model.

PRINCIPLE
Platform Randomised trial of INterventions against COVID-19 In older people





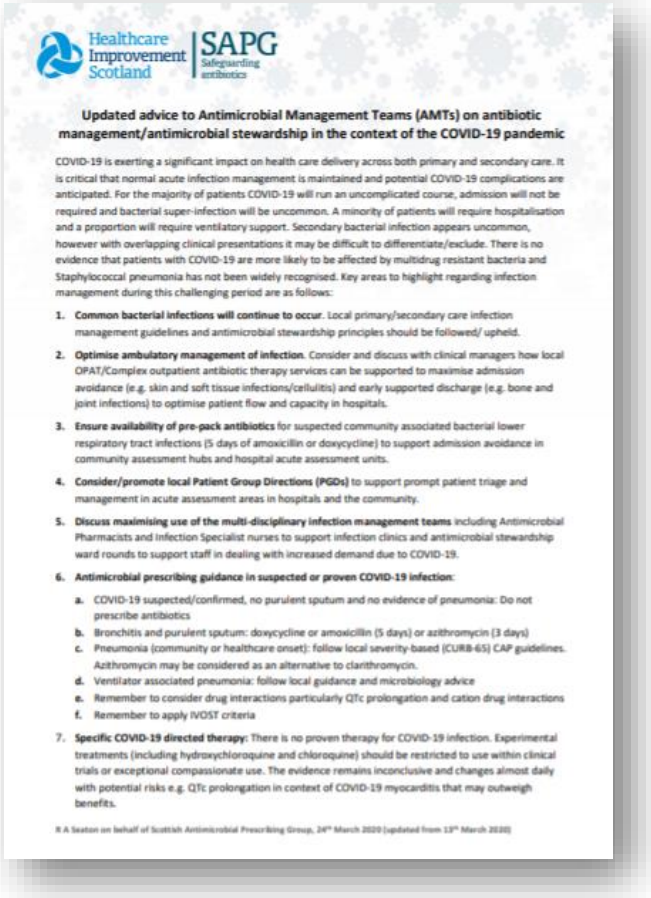
Recovery collaborative group ***Lancet* 2021; 397: 605–12**
Principle Trial Collaborative Group *Lancet* 2021; 397 1063-1074
Butler et al ***Lancet Respir Med*** 2021; 9: 1010–20

RECOGNISE AND REACT

Healthcare Improvement Scotland | SAPG

Safeguarding antibiotics for Scotland, now and for the future

- Maintain and focus national programme
  - Meeting virtually since March 2020
- SAPG guidance for prescribing/ AMS for AMTs 12th and 23rd March
  - Emphasising core AMS principles
    - » Avoid empiric/escalating Abx
    - » WHO Access/ IVOST/ Short duration
- Need to understand prescribing impact
  - Surveillance of antibiotic use
  - Hospitals Point prevalence survey



Healthcare Improvement Scotland | SAPG Safeguarding antibiotics

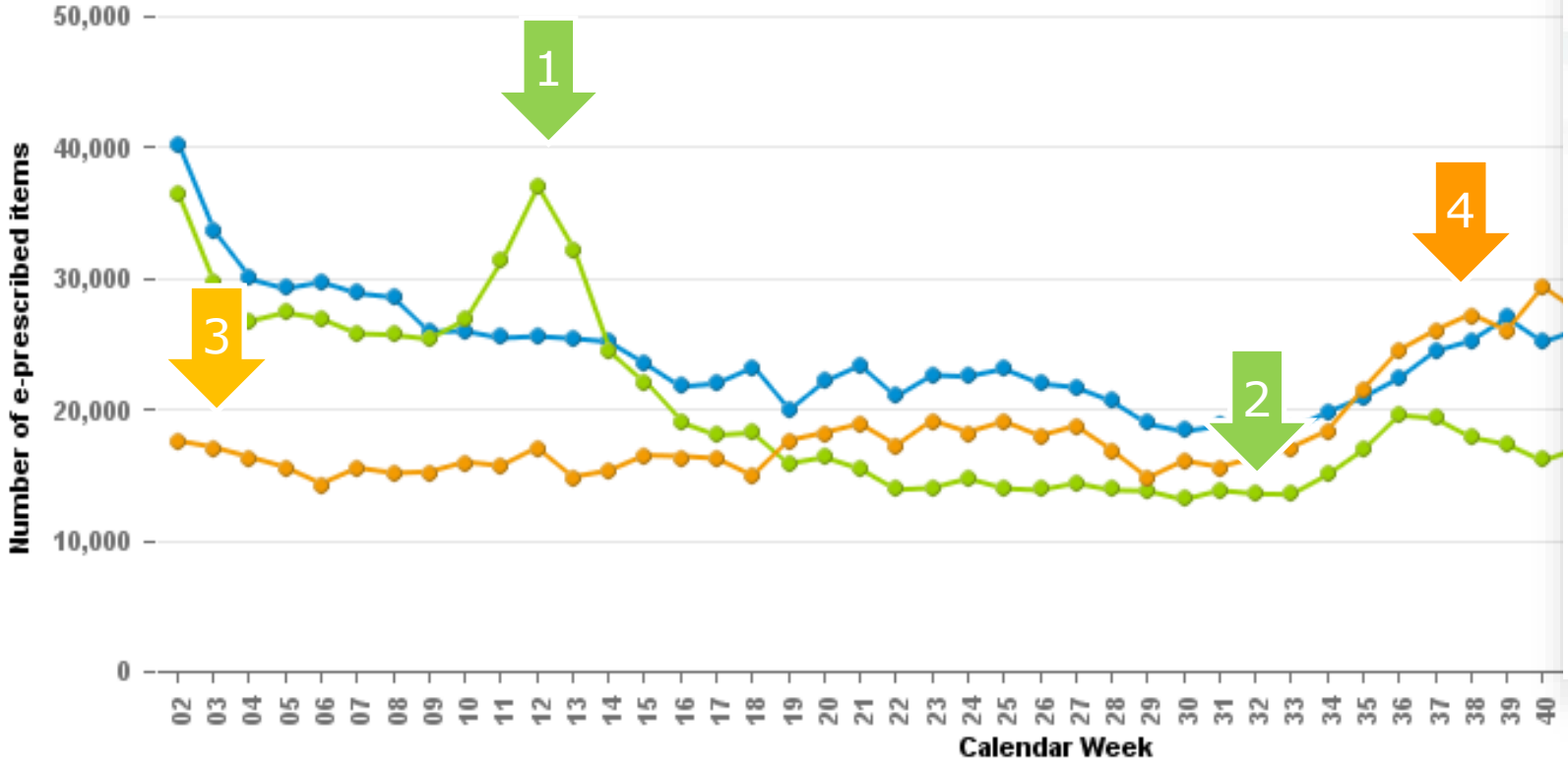
Updated advice to Antimicrobial Management Teams (AMTs) on antibiotic management/antimicrobial stewardship in the context of the COVID-19 pandemic

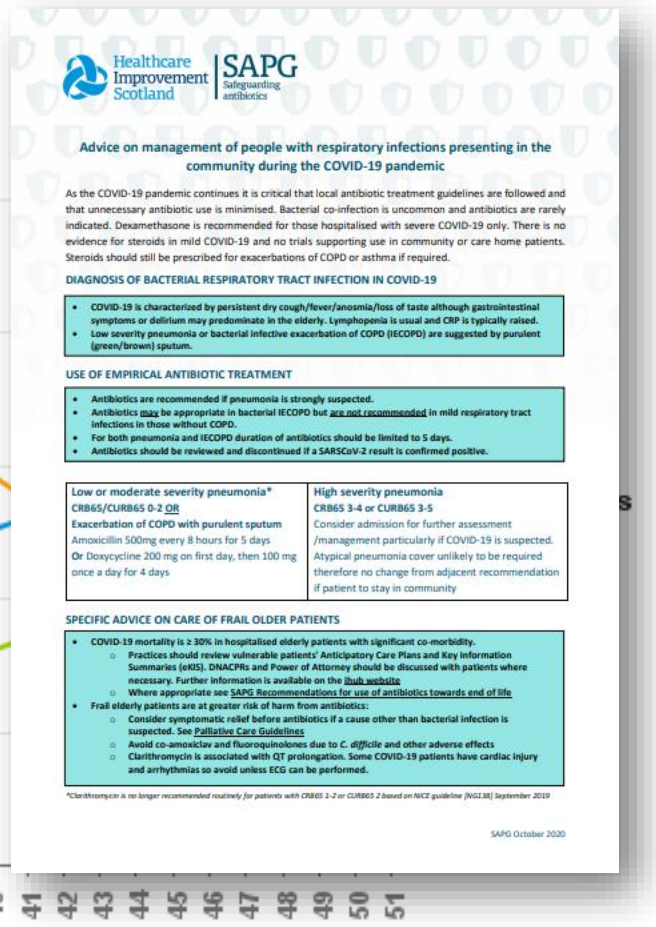
COVID-19 is exerting a significant impact on health care delivery across both primary and secondary care. It is critical that normal acute infection management is maintained and potential COVID-19 complications are anticipated. For the majority of patients COVID-19 will run an uncomplicated course, admission will not be required and bacterial super-infection will be uncommon. A minority of patients will require hospitalisation and a proportion will require ventilatory support. Secondary bacterial infection appears uncommon, however with overlapping clinical presentations it may be difficult to differentiate/exclude. There is no evidence that patients with COVID-19 are more likely to be affected by multidrug resistant bacteria and Staphylococcal pneumonia has not been widely recognised. Key areas to highlight regarding infection management during this challenging period are as follows:

1. **Common bacterial infections will continue to occur**. Local primary/secondary care infection management guidelines and antimicrobial stewardship principles should be followed/ upheld.
2. **Optimise ambulatory management of infection**. Consider and discuss with clinical managers how local OPAT/Complex outpatient antibiotic therapy services can be supported to maximise admission avoidance (e.g. skin and soft tissue infections/cellulitis) and early supported discharge (e.g. bone and joint infections) to optimise patient flow and capacity in hospitals.
3. **Ensure availability of pre-pack antibiotics** for suspected community associated bacterial lower respiratory tract infections (5 days of amoxicillin or doxycycline) to support admission avoidance in community assessment hubs and hospital acute assessment units.
4. **Consider/promote local Patient Group Directions (PGDs)** to support prompt patient triage and management in acute assessment areas in hospitals and the community.
5. **Discuss maximising use of the multi-disciplinary infection management teams** including Antimicrobial Pharmacists and Infection Specialist nurses to support infection clinics and antimicrobial stewardship ward rounds to support staff in dealing with increased demand due to COVID-19.
6. **Antimicrobial prescribing guidance in suspected or proven COVID-19 infection**:
   a. COVID-19 suspected/confirmed, no purulent sputum and no evidence of pneumonia: Do not prescribe antibiotics
   b. Bronchitis and purulent sputum: doxycycline or amoxicillin (5 days) or azithromycin (3 days)
   c. Pneumonia (community or healthcare onset): follow local severity-based (CURB-65) CAP guidelines. Azithromycin may be considered as an alternative to clarithromycin.
   d. Ventilator associated pneumonia: follow local guidance and microbiology advice
   e. Remember to consider drug interactions particularly QTc prolongation and cation drug interactions
   f. Remember to apply IVOST criteria
7. **Specific COVID-19 directed therapy**: There is no proven therapy for COVID-19 infection. Experimental treatments (including hydroxychloroquine and chloroquine) should be restricted to use within clinical trials or exceptional compassionate use. The evidence remains inconclusive and changes almost daily with potential risks e.g. QTc prolongation in context of COVID-19 myocarditis that may outweigh benefits.

R A Seaton on behalf of Scottish Antimicrobial Prescribing Group, 24th March 2020 (updated from 13th March 2020)

Primary Care: Respiratory antibiotics





Healthcare Improvement Scotland | SAPG Safeguarding antibiotics

Advice on management of people with respiratory infections presenting in the community during the COVID-19 pandemic

As the COVID-19 pandemic continues it is critical that local antibiotic treatment guidelines are followed and that unnecessary antibiotic use is minimised. Bacterial co-infection is uncommon and antibiotics are rarely indicated. Dexamethasone is recommended for those hospitalised with severe COVID-19 only. There is no evidence for steroids in mild COVID-19 and no trials supporting use in community or care home patients. Steroids should still be prescribed for exacerbations of COPD or asthma if required.

DIAGNOSIS OF BACTERIAL RESPIRATORY TRACT INFECTION IN COVID-19

- COVID-19 is characterized by persistent dry cough/fever/anosmia/loss of taste although gastrointestinal symptoms or delirium may predominate in the elderly. Lymphopenia is usual and CRP is typically raised.
- Low severity pneumonia or bacterial infective exacerbation of COPD (IECOPD) are suggested by purulent (green/brown) sputum.

USE OF EMPIRICAL ANTIBIOTIC TREATMENT

- Antibiotics are recommended if pneumonia is strongly suspected.
- Antibiotics may be appropriate in bacterial IECOPD but are not recommended in mild respiratory tract infections in those without COPD.
- For both pneumonia and IECOPD duration of antibiotics should be limited to 5 days.
- Antibiotics should be reviewed and discontinued if a SARSCoV-2 result is confirmed positive.

Low or moderate severity pneumonia* CRB65/CURB65 0-2 OR Exacerbation of COPD with purulent sputum	High severity pneumonia CRB65 3-4 or CURB65 3-5
Amoxicillin 500mg every 8 hours for 5 days Or Doxycycline 200 mg on first day, then 100 mg once a day for 4 days	Consider admission for further assessment /management particularly if COVID-19 is suspected. Atypical pneumonia cover unlikely to be required therefore no change from adjacent recommendation if patient to stay in community

SPECIFIC ADVICE ON CARE OF FRAIL OLDER PATIENTS

- COVID-19 mortality is ≥ 30% in hospitalised elderly patients with significant co-morbidity.
  - Practices should review vulnerable patients' Anticipatory Care Plans and Key Information Summaries (eKIS). DNACPRs and Power of Attorney should be discussed with patients where necessary. Further information is available on the ihub website
  - Where appropriate see SAPG Recommendations for use of antibiotics towards end of life
- Frail elderly patients are at greater risk of harm from antibiotics:
  - Consider symptomatic relief before antibiotics if a cause other than bacterial infection is suspected. See Palliative Care Guidelines
  - Avoid co-amoxiclav and fluoroquinolones due to *C. difficile* and other adverse effects
  - Clarithromycin is associated with QT prolongation. Some COVID-19 patients have cardiac injury and arrhythmias so avoid unless ECG can be performed.

*Clarithromycin is no longer recommended routinely for patients with CRB65 1-2 or CURB65 2 based on NICE guideline [NG138] September 2019

SAPG October 2020

ARHAI Scotland
Antimicrobial Resistance and Healthcare Associated Infection

*amoxicillin, doxycycline, clarithromycin, Azithromycin and co-amoxiclav

Fiona McQueen, Chief Nursing Officer
Gregor Smith, Chief Medical Officer
Alison Strath, Chief Pharmaceutical Officer

Scottish Government
Riaghaltas na h-Alba
gov.scot

NHS Board Chief Executives
Copy : NHS Board Chairs, Medical Directors,
Nursing Directors and Directors of Pharmacy

23 November 2020

Dear colleagues,

Antimicrobial Stewardship during the Covid-19 pandemic

We in Scotland have a strong record on Antimicrobial Stewardship (AMS), with encouraging and positive trends reported in the 'Scottish One Health Antimicrobial Use and Antimicrobial Resistance Report' that was published on 17 November. However, we are writing to draw your attention to two ways in which the Covid-19 pandemic may adversely affect our efforts to maintain good AMS and contain and control Antimicrobial Resistance (AMR).

Firstly, it is clear that Covid-19 has had, and is likely to continue to have, an impact on antibiotic prescribing decision-making across all sectors of care.

Published evidence to date does not support significant risk of bacterial co-infection with SARS-CoV-2 in community managed patients, nor in those receiving ward care in hospitals. However, cumulative antibiotic exposure may increase the risk of secondary infections (including infection with antimicrobial resistant organisms) in those with severe Covid-19 illness and particularly those in the critical care setting.

Other unintended consequences of cumulative antibiotic exposure include, but are not limited to, risk of *C. difficile* infection and infections associated with antimicrobial resistant organisms.

The Scottish Antimicrobial Prescribing Group have produced up-to-date recommendations for both primary care and hospitals, to support best antibiotic prescribing practice and antimicrobial stewardship to limit unnecessary prescribing during the pandemic. Please take note of these:

Advice on community respiratory infections and COVID-19
Advice on hospital Antimicrobial Stewardship COVID-19

Secondly, we reiterate the critical need for continued focus on preventing infection transmission risks in all healthcare settings. There have been observed increases in the rates of healthcare associated infection during the pandemic period, and this also has important implications for containment of AMR.

At this time, with the focus rightly on Covid-19, we seek your ongoing support in ensuring that patients continue to be assessed for all infection risks. This includes the application of the mandatory MRSA and CPE admission screening policies, as set out in the National Infection Prevention and Control Manual:

http://www.nipcm.hps.scot.nhs.uk/

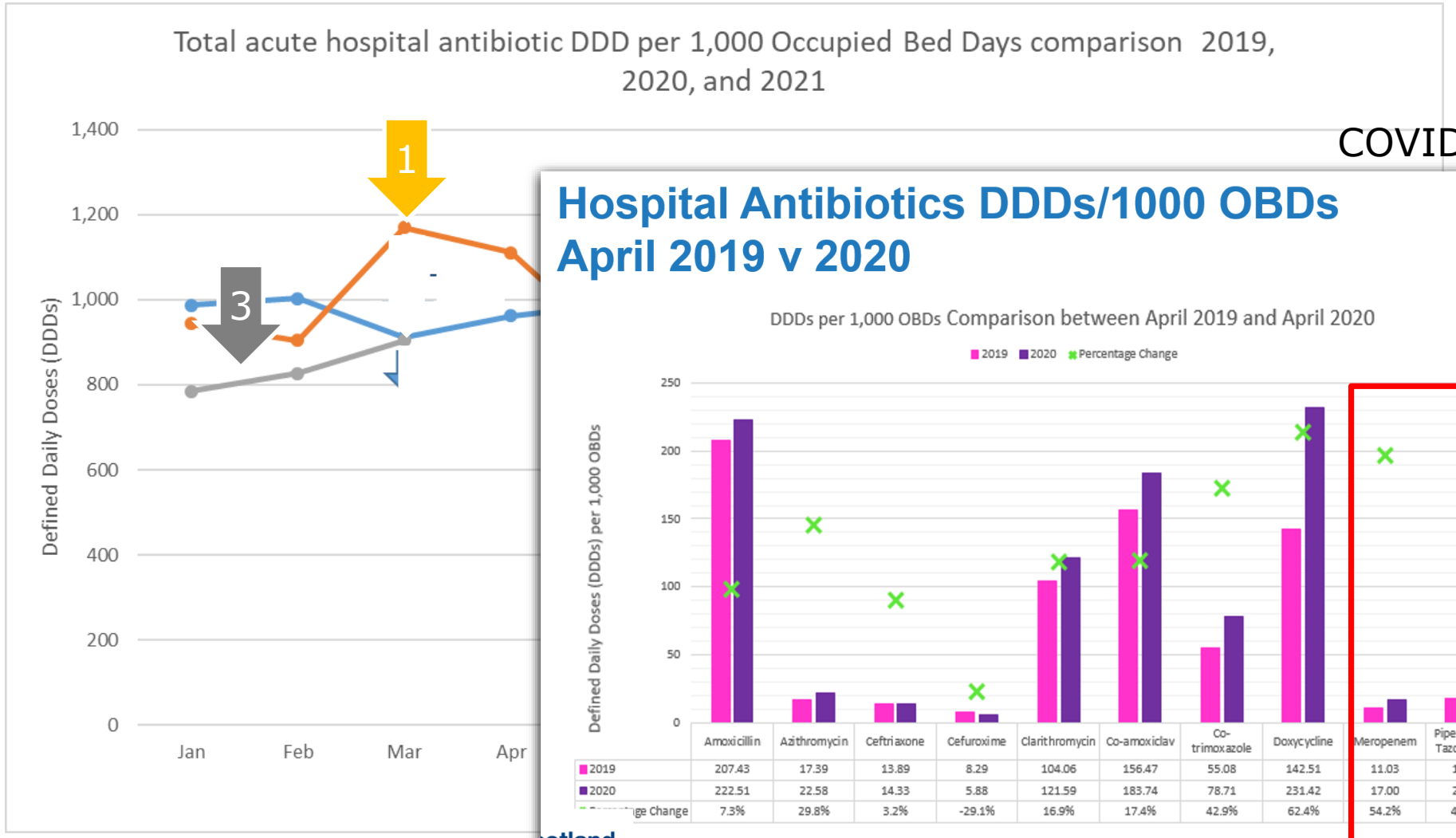
We would be grateful if you could cascade as appropriate to clinical teams.

Thank you.

Kind regards,

Fiona McQueen **Gregor Smith** **Alison Strath**

Secondary Care: All Antibiotics (DDDs/1000 OBDs)



COVID-19 wave peaks

Hospital Antibiotics DDDs/1000 OBDs April 2019 v 2020

	Amoxicillin	Azithromycin	Ceftriaxone	Cefuroxime	Clarithromycin	Co-amoxiclav	Co-trimoxazole	Doxycycline	Meropenem	Piperacillin + Tazobactam
2019	207.43	17.39	13.89	8.29	104.06	156.47	55.08	142.51	11.03	18.18
2020	222.51	22.58	14.33	5.88	121.59	183.74	78.71	231.42	17.00	26.41
Change	7.3%	29.8%	3.2%	-29.1%	16.9%	17.4%	42.9%	62.4%	54.2%	45.3%

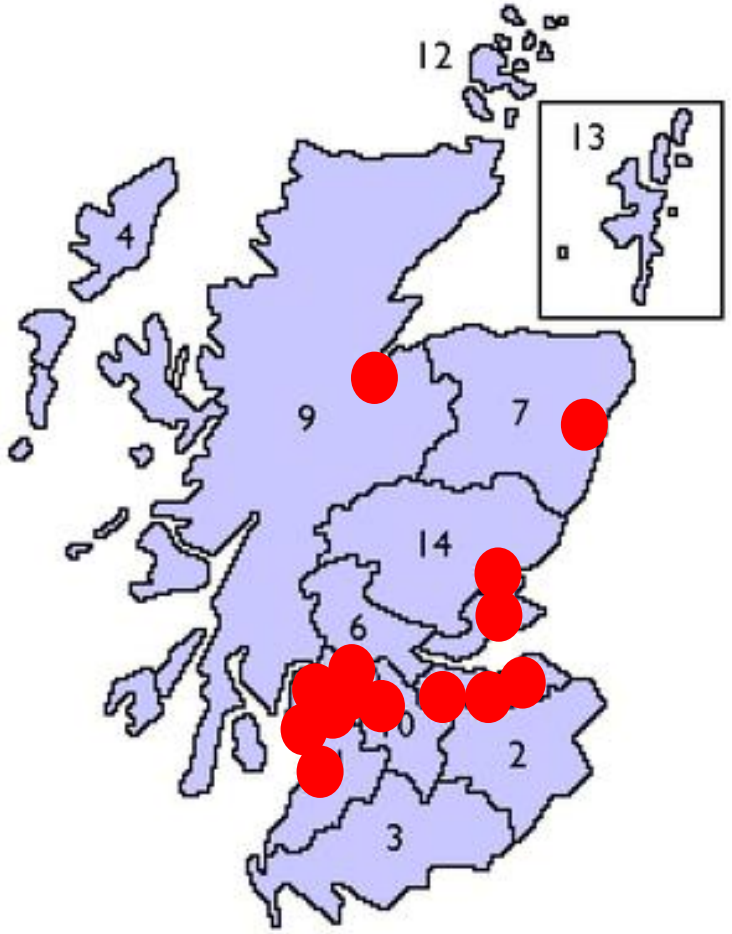
Acknowledgement: Billy Malcolm

Point Prevalence Survey

- AMTs invited all Scottish HBs
  - 15 Hospitals
  - 112 COVID-19 units
  - Single day 20th - 30th April 2020

  - 820 pts (531 SARS-CoV-2 +ve)
  - 37% of national IPs
  - 52% male, median age 71 yrs
  - 15% Critical care

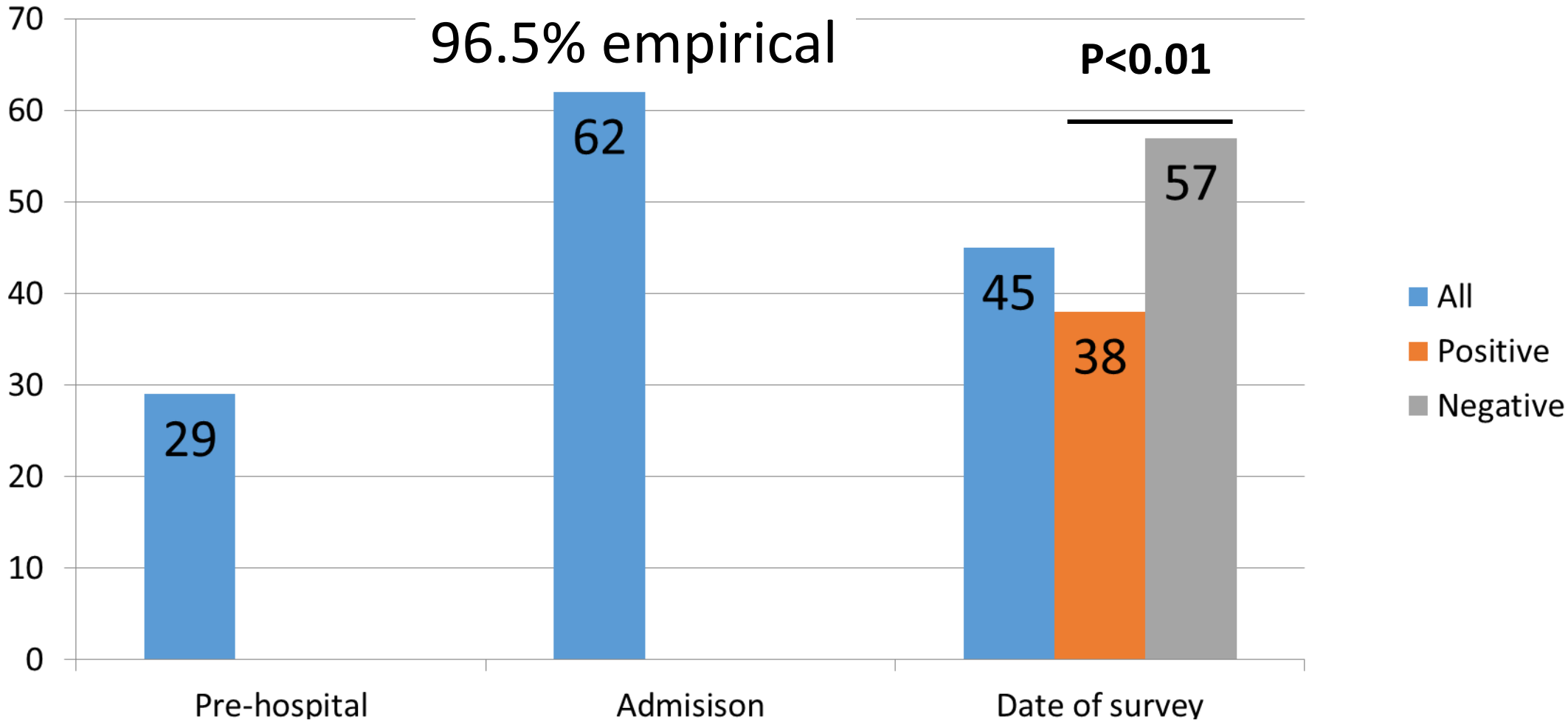
22.1% Probable/Definite HAI



Seaton et al J Infection 2021

Antibiotics prescribed

74%: ?RTI



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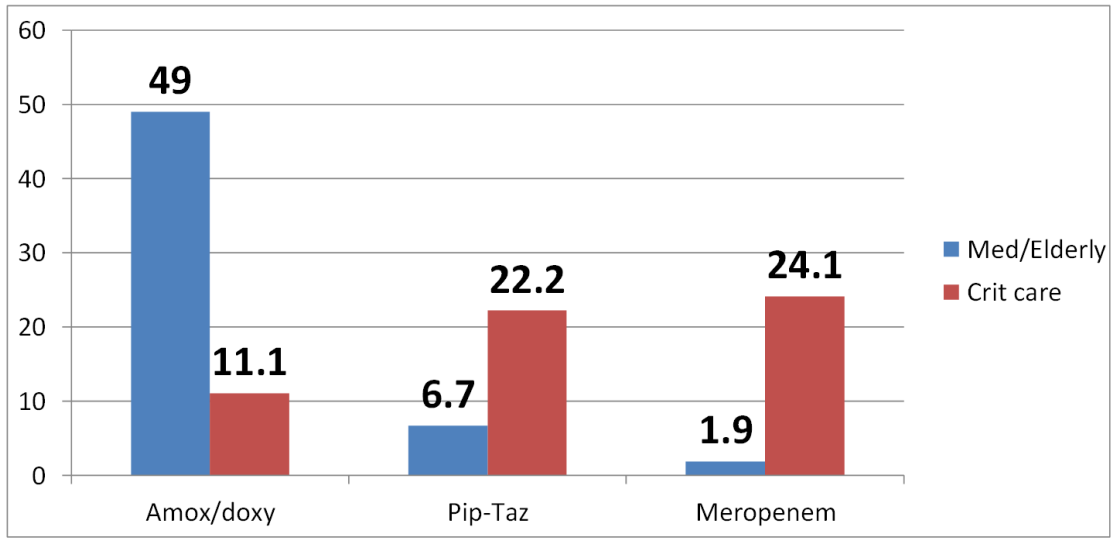
Factors associated with a prescription of antibiotic on day of survey in those with suspected RTI (all patients)

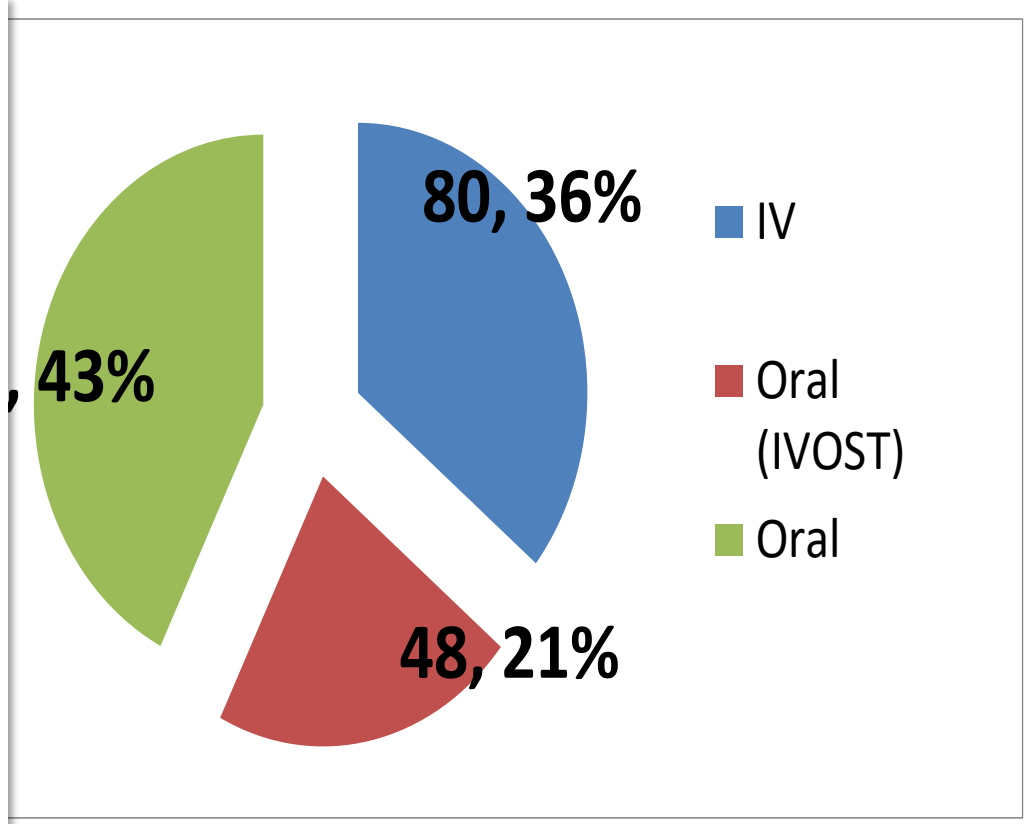
Variable	OR	Lower 95% CI	Upper 95% CI	Wald test p-value
SARS-CoV-2 positive	0.51	0.33	0.81	0.005
COPD/Chronic lung disease	2.40	1.66	3.46	<0.001
Diabetes	0.58	0.40	0.84	0.006
CRP ≥ 100 mg/l	1.83	1.28	2.61	0.001
Abnormal Chest X-ray	1.88	1.22	2.90	0.005
Purulent or bloody Sputum	1.85	1.17	2.91	0.01
Probable or definite nosocomial COVID-19	0.43	0.24	0.74	0.004

Seaton et al, JAC-AMR, 2021

Prescribing indicators for RTI antibiotics on day of survey (ward patients)

Differences between Wards and Critical care

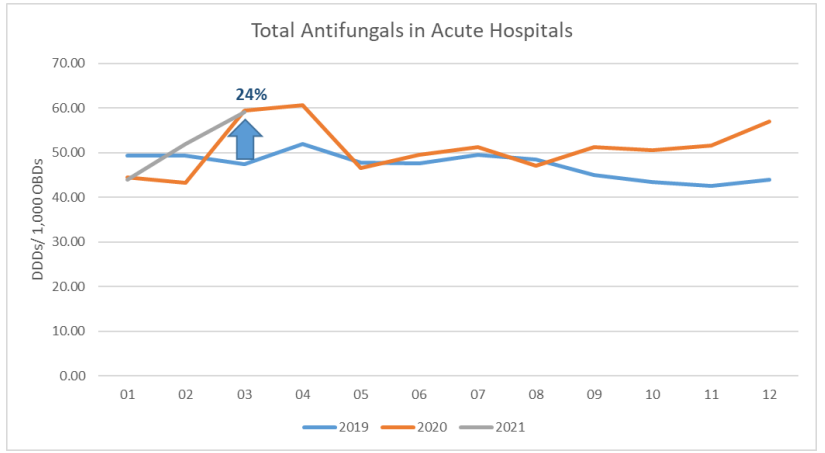




Seaton et al, JAC AMR 2021

Systemic Antifungal Prescribing

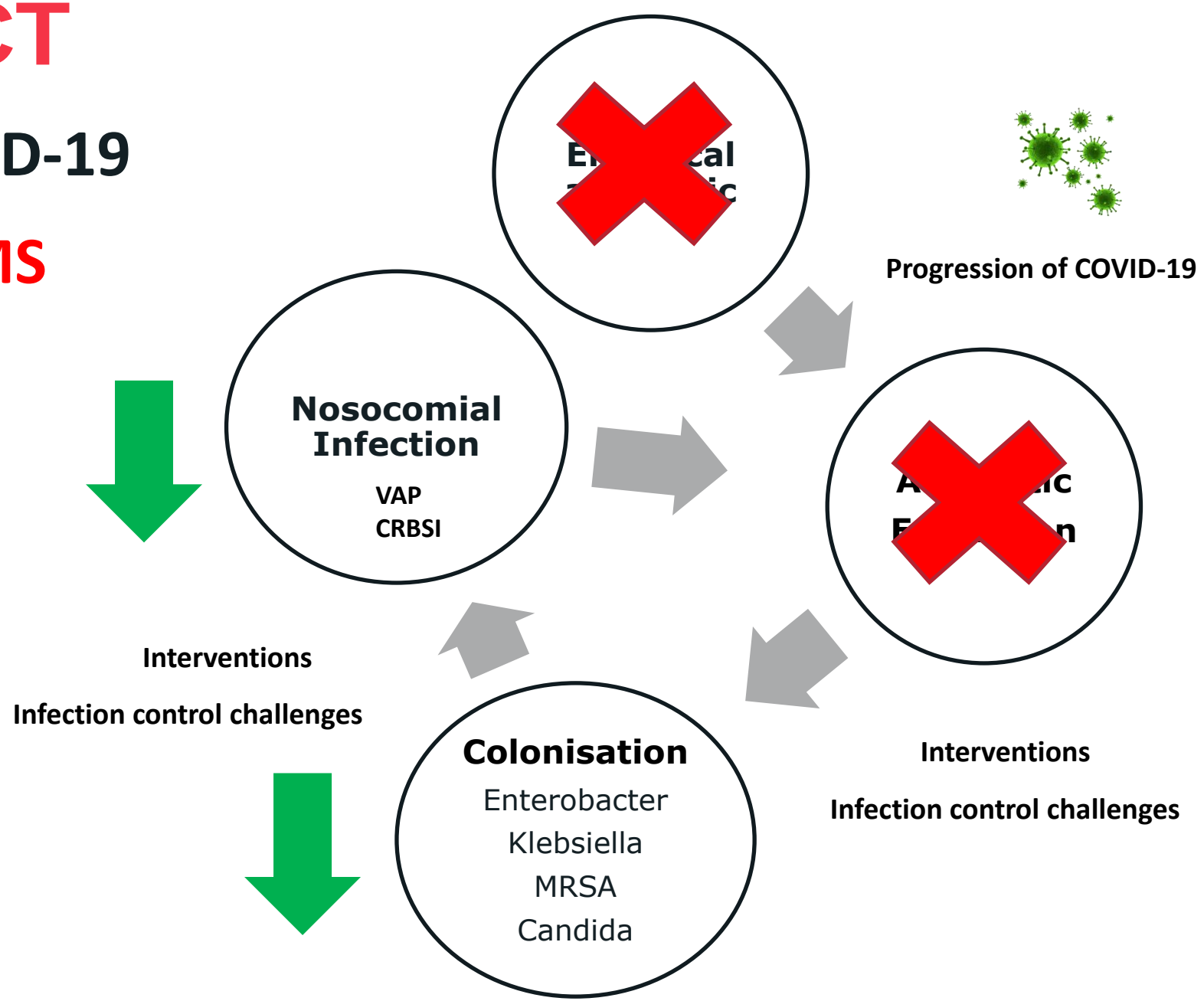
- 9.8% in critical care
- Median 19 days post admission (IQR 16.5 – 20)
- Median 18 days post admission to critical care
- **All** on RESERVE antibiotics



REFLECT

COVID-19

+ AMS



Antimicrobial Prescribing in Suspected/ Proven COVID-19

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Empiric Rx

- Avoid empirical antibiotic Rx in suspected/proven COVID-19
- Don't use CRP to guide
- WHO Access if required and limit/record duration

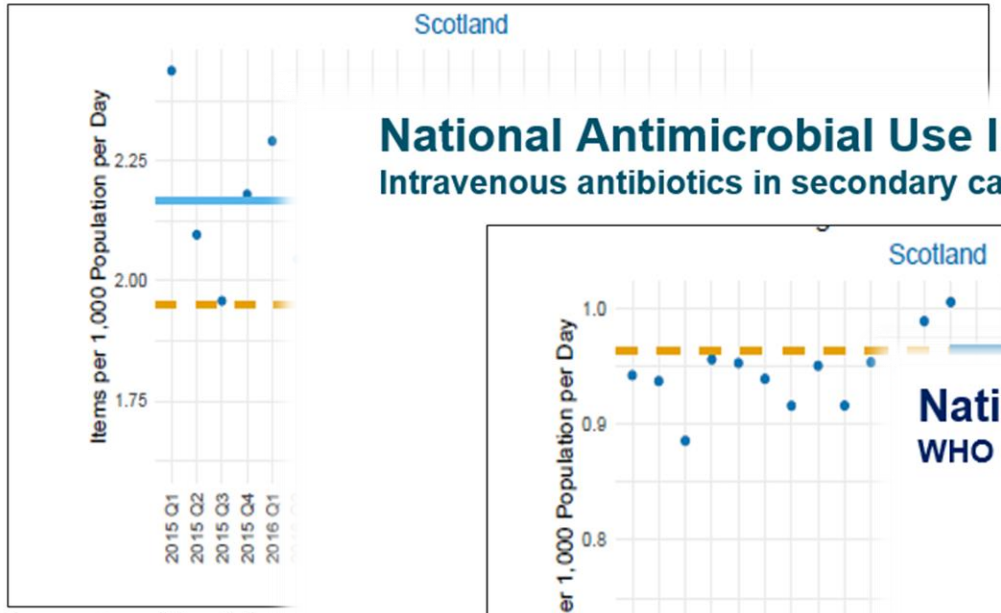
Review

- Consider stopping antibiotics following positive SARS-CoV-2 result
- Avoid antibiotic escalation outside of critical care
- Optimise micro sampling (particularly critical care)
- PCT in critical care – guide de-escalation/stopping
- Limit duration and optimise IVOST

https://www.sapg.scot/about-us/latest-updates/updated-advice-on-covid-19/

National Antimicrobial Use Indicator 1:

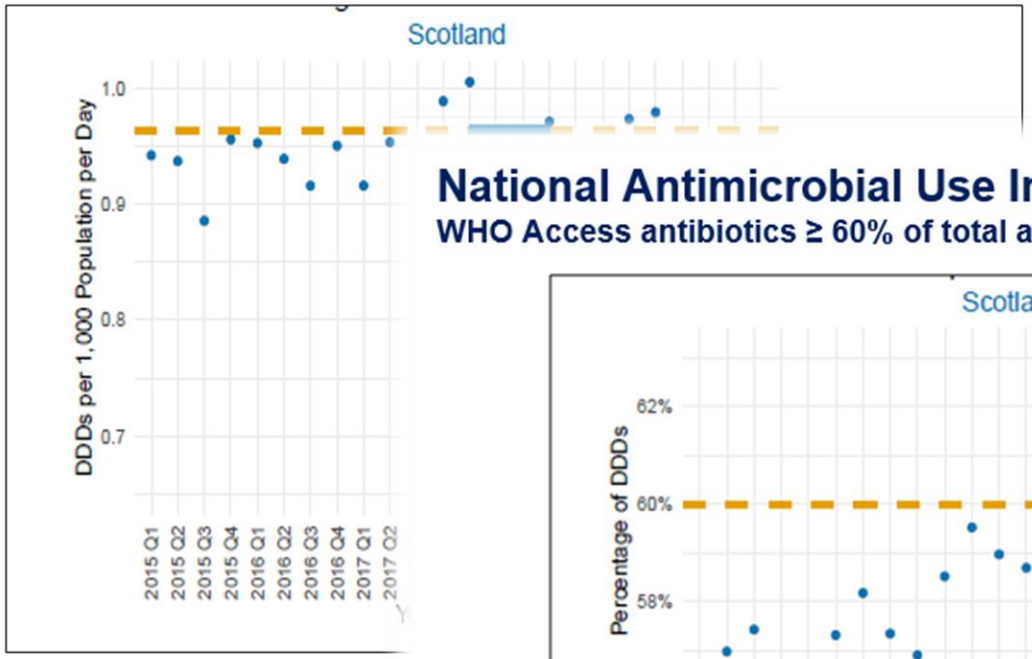
10% reduction antibiotic use in Primary Care (excluding dental) by 2022, using 2015 as baseline



Source: Prescribing Inform
Scotland

National Antimicrobial Use Indicator 2:

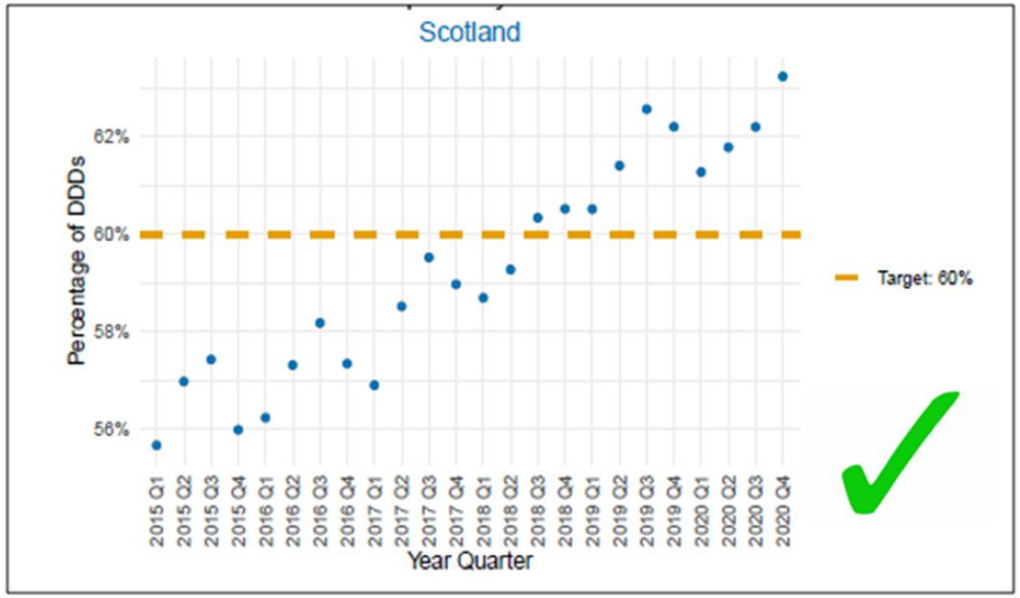
Intravenous antibiotics in secondary care no higher in 2022 than in 2018



Source: Hospital Medicines Utilisation Database, NHS Nati
2020 Q3 includes only partial data for NHS Borders (2% of Scottish P
(3% of population), 2020 Q4 contains only partial data for NHS West

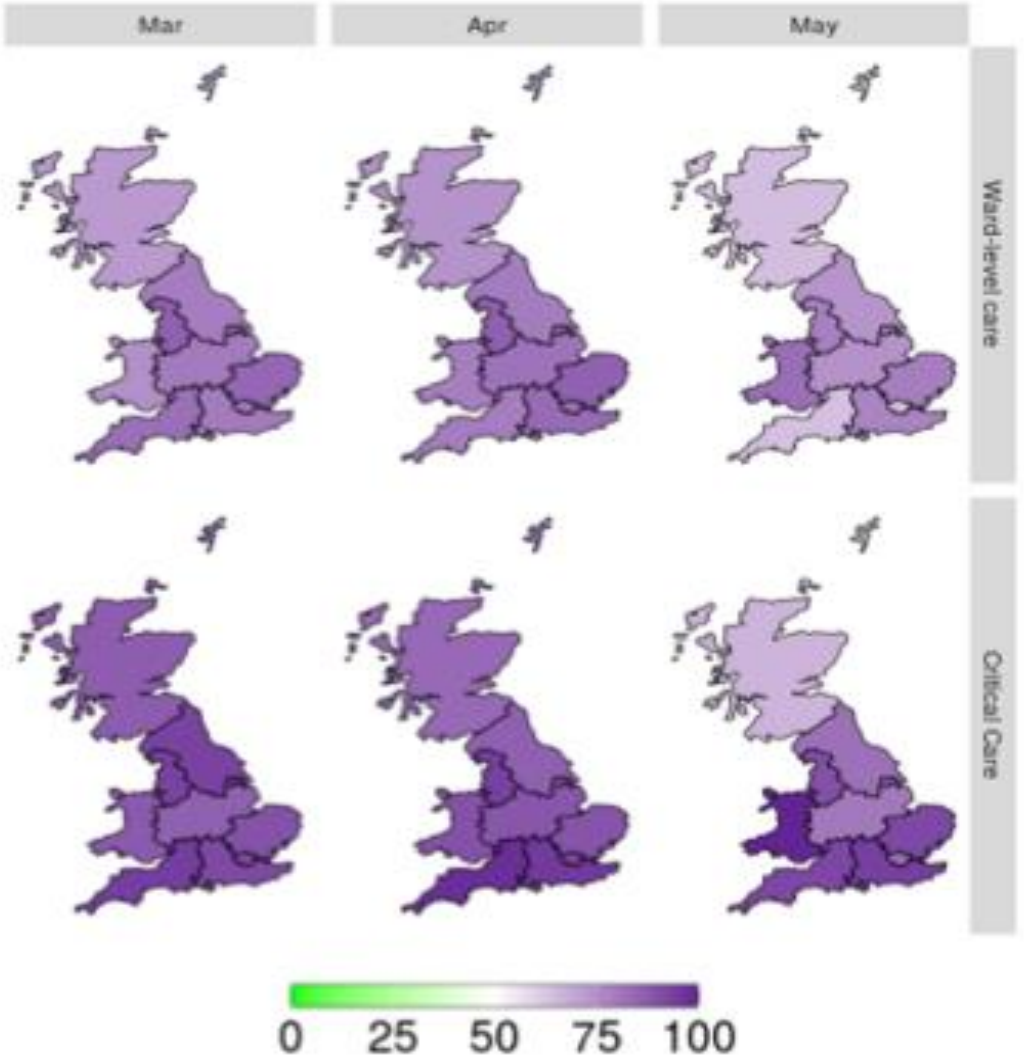
National Antimicrobial Use Indicator 3:

WHO Access antibiotics ≥ 60% of total antibiotic use in Acute hospitals by 2022



Source: Hospital Medicines Utilisation Database, NHS National Services Scotland and Public Health Scotland
2020 Q3 includes only partial data for NHS Borders (2% of Scottish Population), 2020 Q4 contains no data for NHS Borders (2% population), and NHS Dumfries & Galloway (3% of population), 2020 Q4 contains only partial data for NHS Western Isles (0.5% population), and NHS Shetland (0.4% population).

UK Regional differences in prescribing in hospitalised COVID-19 patients during first wave

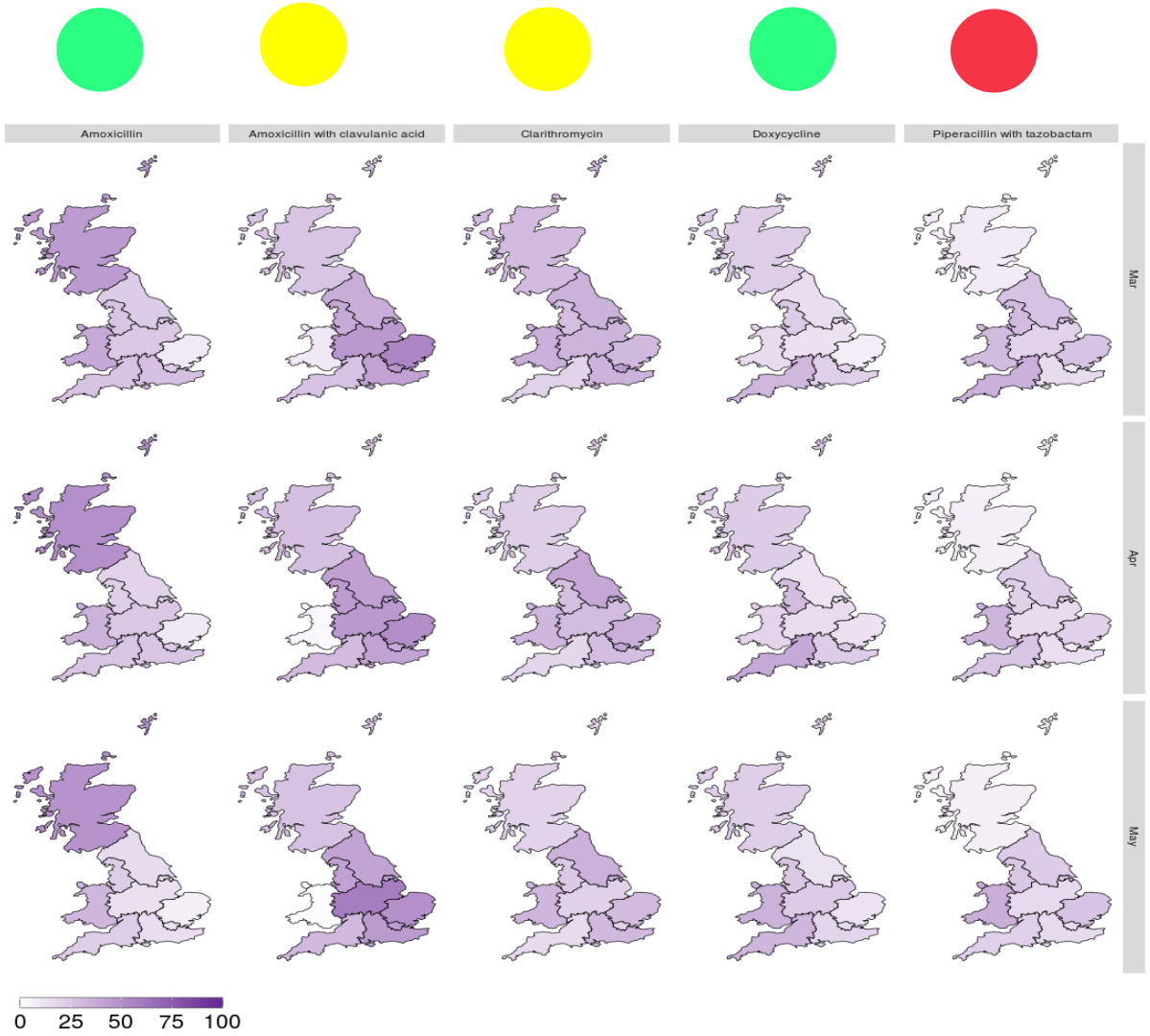


Geographical variation in antimicrobial usage over time

Purple shading of regions represents the percentage of patients who received antimicrobial therapy during their hospital admission, stratified by month of admission (March, April and May) and by level of care (ward-level or critical care).

Russell et al Lancet microbe 2021 https://doi.org/10.1016/ S2666-5247(21)00090-2

Regional differences in prescribing in hospitalised COVID-19 pts during first wave: Specific agents



Geographical variation in usage of individual antimicrobials over time

Purple shading of regions represents the percentage of patients who received the named antimicrobial during their hospital admission stratified by month of admission (March, April and May). **(a)** shows patients in critical care and **(b)** shows patients receiving ward-level care.

Russell et al Lancet microbe 2021 https://doi.org/10.1016/ S2666-5247(21)00090-2

Summary

- Significant challenges on local/national level
- National programme recognised, reacted and reflected and now resetting
- Importance of information, feedback and engagement and collaboration with AMTs and HCPs more widely
- Focus on key AMS principles

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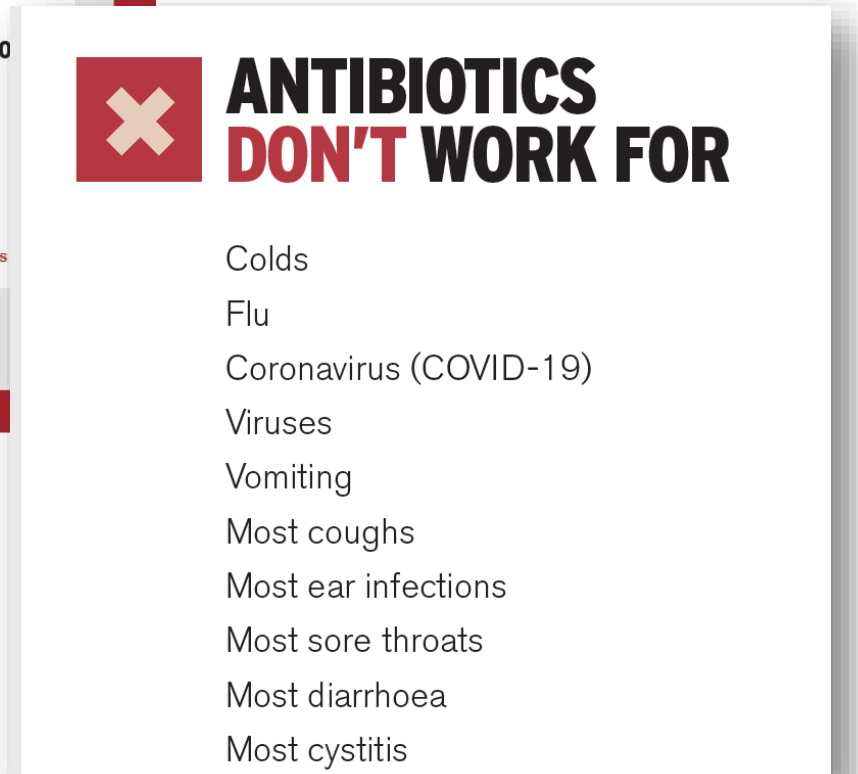

Acknowledgements

- Jacqui Sneddon, Billy Malcolm, Lesley Cooper, Marion Pirie and Cheryl Gibbons

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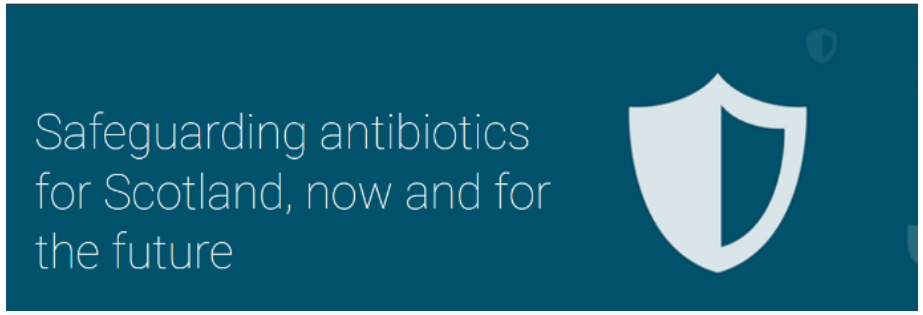

The authors would like to thank health board Antimicrobial Management Teams and clinicians in the participating hospitals who coordinated the survey and collected data: Ursula Altmeyer, Natalie Arandia, Francisca Bartilottimatos, Vhairi Bateman, Andrew Blunsum, Kevin Blythe, Sarah Bowers, Rhona Boyle, Adam Brown, Mark Brown, Niamh Burns, Robyn Canham, Sadman Chowdhury, Katherine Cobb, Alison Cockburn, Malcolm Daniel, Peter Davies, Gilchrist Docherty, Thomas Downs, Morgan Evans, Eoghan Farmer, Leonard Farrugia, Jude Fleming, Stewart Gallagher, Claire Gilmore, Anna Graham, Jane Gravil, Hudson Guyver, Phil Henderson, Lisa Hutton, Katherine Hylands, Su Su Htwe, Caitlin Hughes, Callum Innes, Alistair James, Cameron Kay, Elena Kay, Heather Kennedy, Laura Knox, Nicole Lau, Andrew Lazarowicz, Eilidh Lynch, Alison MacDonald, Mhairi Mactier, Sumera Mahmood, Thalia Massa, Kaitlin Mayne, Catriona McBride, Dayni McConnell, Steve McCormick Marcus McClean Fiona McDonald, Dominic McGovern, A McGucken, Andrew McKay, Jo McEwan, Lara Mitchell, Olivia Morton, Samantha Ong, Dominic Owtram, Espe Palenzuela, Rebecca Petrie, Carol Philip, Kimberley Phillip, Niketa Platt, Nathaniel Quail, Emily Reid, Stuart Reid, Mathew Robinson, Laura Quate, K Rajasegaran, Jen Rollo, Claire Rooney, Kevin Rooney, Maggie Rostron, Chris Salt, Andrew Smart, Lee Stewart, Harrison Stubbs, Bobby Sykes, Daniel Taylor-Sweet, Harriet Turner, Jennifer Wardall, Emily Wright, Caitlin Young. Thanks also to Marion Pirie, SAPG Project Officer for supporting all communications associated with the study.