Analysis in Comparative Study on Antimicrobial Stewardship and Antibiotic Prescribing: 2019 vs. 2020 COVID-19 Era

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Phase 1: Systematic Literature Review

Antimicrobial stewardship implementation before and during the COVID-19 pandemic in the acute care settings: a systematic review

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This systematic review analysed data from over 63,921 patients who received antibiotics in acute care settings between 2000 and 2021. The goal was to explore strategies and measures for AMS implementation. It was found that overuse and irrational use of antimicrobials is a significant problem for healthcare, which can lead to negative impacts on patient safety, the emergence of antibiotic resistance, and increased economic burden (ECDC, 2019; Dadgostar, 2019). The majority of respiratory tract infections, particularly Upper Respiratory Tract Infections (URTIs), are caused by viruses but are often treated with antimicrobials (Li et al., 2016). There is a lack of strong evidence supporting AMS implementation, which has led to
confusion and disagreement about their effectiveness. This high antimicrobial consumption in COVID-19 patients was initiated after early reports from China revealed that 50% of patients died from secondary bacterial infection (Lucien et al., 2021; Shallal et al., 2022). A range of AMS interventions has been reviewed in the US IDSA guidelines and BSAC stewardship practical guide in the UK (Dellit et al., 2017; BSAC, 2018). When establishing a new stewardship program, it is best to start with the core strategies and focus on achieving and maintaining them before adding some supplemental strategies.

Antimicrobial Stewardship Core Strategies

Two core ASP strategies have emerged: front-end strategies, which involve an approval process for making antimicrobials available (formulary restrictions and pre-authorization), and back-end strategies, which involve reviewing antimicrobial use after therapy has been initiated (prospective audit with intervention and feedback). A review of these strategies found that back-end strategies, although more labour-intensive, are more widely practised, more readily accepted by clinicians, and provide more educational opportunities, leading to a more sustained impact on improving antimicrobial prescribing quality (BSAC, 2019). The front-end strategy used PP in 54% of studies, while the back-end strategy was used in 85% of all studies and two studies DP (Spernovasilis et al., 2021; Ashiru-Oredope et al., 2021).

Multidisciplinary Team: A multidisciplinary AMS team was found in most of the included studies, 92%. It was considered one of the key components of the structure and governance of the AMS. It consists of a core membership of an infectious disease physician (or lead doctor or physician champion), a clinical microbiologist, and a clinical pharmacist with expertise in infection (Supplementary Figure S2). Other members could be specialist nurses, for example, infection prevention or stewardship nurses, quality improvement or risk management or patient safety managers, and clinicians interested in infection. The multidisciplinary AMS team should perform a gap analysis of antimicrobial use at the facility to identify priority areas for improvement and set up a plan for AMS implementation and measurement (BSAC, 2019).

Formulary Restrictions and Pre-authorization: The study was conducted in Pennsylvania and compared the change from the pre-authorisation AMS strategy to the prospective audit with feedback. There was a significant increase in the use of the affected antimicrobials and the overall use of all antimicrobial agents. During the preintervention period, both total systemic antimicrobial use (~9.75 DOT/1,000-PD per month) and broad-spectrum anti-gram-negative antimicrobial use (~4.00 DOT/1,000-PD) declined (Mehta et al., 2014). Another study was conducted in Massachusetts. It aimed to study the new restriction methods, such as Front-End Back End, Automatic Stop Orders, ID Consult and Verbal Approval. It included a list of restricted antimicrobial agents (broad spectrum and later generation antimicrobials), such as New Specific
Medication Restrictions: Anti-Pseudomonas, Carbapenems, Tigecycline, Vancomycin, Colistin, Daptomycin, Linezolid, Antifungals, Fluoroquinolones. The result of this study indicated that Daptomycin and Linezolid were the most frequently restricted antimicrobials (Weston et al., 2013). An interesting study conducted in India evaluating the use of the justification form to prescribe restricted antimicrobials, such as colistin, polymyxin B, tigecycline, intravenous (IV) minocycline, IV fosfomycin, daptomycin & echinocandins (caspofungin, micafungin & anidulafungin) found that prescribing any of these antimicrobials necessitated filling an antimicrobial justification form, which was then sent to the AMS multidisciplinary committee. These forms were tallied with a daily indent list of restricted antimicrobials from the pharmacy, and any missing forms were requested to be submitted. At 48–72 hours from the time of prescription, the AMS committee for review (Thakkar et al., 2021).

**Antibiotic Review:** The antibiotic review was one of the effective AMS strategies PP and DP. It was found in 69% (9 of 13) of the included studies. Antibiotic review could be conducted after 24 hours (Day 1) of prescribing the antibiotics. It included a review of the doses and the possibility of an IV-to-oral switch. It also could be conducted on Day 4 to review appropriateness considering microbiological culture results or on Day 7 to review the duration of therapy (BSAC, 2019). We found that the antibiotic review 48–72 Hours from the time of prescription was conducted by microbiology (Surat et al., 2021) or the AMS multidisciplinary committee (Thakkar et al., 2021). Interestingly, the use of the Team Antibiotic Review Form (TARF) Document by frontline prescribers was significant in decreasing antibiotic use. It was used in conjunction with antibiotic stewards for patients actively receiving antibiotics to facilitate discussions about appropriate antibiotic prescribing using the Four Moments framework: A) Make the diagnosis; B) Cultures and Empiric Therapy; C) Stop, Narrow; D) Change to Oral antibiotics; E) Duration. The use of promotional and attractive materials to promote the Four Moments of Antibiotic Decision-Making, such as posters, pocket cards, and screen savers, to advertise the Four Moments Framework. Antibiotic use was decreased by 30.3 DOT per 1000 PD (95% CI, −52.6 to −8.0 DOT; P = .008). Additionally, the incidence rate of hospital-onset C difficile laboratory-identified events decreased by 19.5% (95% CI, −33.5% to −2.4%; P = .03) (Tamma et al., 2021). Interestingly, in the study conducted in the UK, 58 UK acute hospital organisations expressed an interest in participating. In England, the Department of Health's guidance Start Smart—Then Focus required prescribers to review and revise antibiotic prescriptions every 48–72 h.12. In the USA, the analogous term antibiotic timeouts are used. Still, revised CDC guidance in 2019 prioritised pharmacist-led audits and feedback to prescribers. This study aimed to evaluate a multifaceted behaviour change intervention, i.e., the Antibiotic Review Kit (ARK), designed to reduce antibiotic use among adult acute general medical inpatients by increasing appropriate decisions to stop antibiotics at clinical review. It focused on decisions to stop rather than decisions to start antibiotics.

**Prospective Audit and Feedback:** Another study was conducted in Greece. It was focused on the prescription of carbapenems with regard to the indication, dosage, age and duration of treatment, combined with the judicious use of carbapenem-sparing antibiotics whenever appropriate. The programme is based on the prospective audit and feedback strategy, along
with a case-based education of treating doctors. An infectious diseases (ID) specialist and an ID fellow are being alerted by the hospital pharmacy upon prescription request for carbapenem and provide unsolicited in-person (“handshake”) consultation within 72 h for all patients for whom the treating doctors have prescribed carbapenem. The antibiotic review and ward rounds. Further ID consultation service upon request is available seven days a week, 24 hours a day, through telephone or in-person (Spernovasilis et al., 2021).

**Antimicrobial Stewardship Supplemental Strategies**

The Streamlining/timely de-escalation of therapy strategy was found in five studies PP and only one study DP (Ashiru-Oredope et al., 2021). This strategy was implemented with an antimicrobial timeout of 48 hours. It consists of re-evaluating the patients’ empirical and/or definitive antimicrobial regimen, after which the antimicrobials were either continued, escalated or de-escalated according to the patient's clinical condition. This strategy was also part of the regular prospective audit and feedback, where the data-recording team kept track of the timelines and doctors in charge regarding timeout for each patient (Panditrao et al., 2021). Antibiotic de-escalation strategy in Community-Acquired Pneumonia (CAP) was one of the AMS activities that were significantly affected by the COVID-19 pandemic (Ashiru-Oredope et al., 2021) (Table 3.5 Figure 3.1).

Both dose optimisation/antibiotic dose adjustment and parenteral-to-oral conversion protocols showed significant outcomes with P-values of 0.03 and 0.04, respectively, in the multi-centre study of California – US, which included 422 general acute care hospitals (Trivedi et al., 2013). During the pandemic, dose optimisation could be used for the specific antibiotic, such as Carbapenems, which focused only on the prescription of carbapenems with regard to the indication, dosage and duration of treatment, combined with the judicious use of carbapenem-sparing antibiotics whenever appropriate. This approach was an essential part of AMS implementation DP (Spernovasilis et al., 2021). Additionally, in the study assessing the Impact of COVID-19 on Antimicrobial Stewardship Activities/Programs among HCPs in the United Kingdom, respondents were concerned about increased antibiotic use, including increased use of broad-spectrum antibiotics, delayed parenteral-to-oral switch (Ashiru-Oredope et al., 2021).

Guidelines and Clinical Pathways were the most used, as they were applied in 69% PP and DP. However, the organisational collaboration in applying the AMS guidelines and clinical pathways strategy was effectively implemented during the pandemic (Ashiru-Oredope et al., 2021; Williams et al., 2021). In addition, adherence to the local, national, and international guideline recommendations is vital to prevent over- and inappropriate prescribing of antimicrobials. During the pandemic, we found that the availability of updated antimicrobial guidelines, such as the NICE, as well as international guidelines from the WHO and the International Pharmaceutical Federation (FIP), were highly effective. The management of clinical pathways, such as pneumonia and respiratory tract infections in COVID-19 patients, should also be updated.
Additionally, the local or organisational clinical practice guidelines should be adapted based on the local antibiograms and resistogram in order to maintain the relevance of the antimicrobial guidelines, as recommended, which has an essential role in decreasing the inappropriate use of antibiotics and decreasing the AMR (Surat et al., 2021).

In Scotland, Concern regarding bacterial co-infection complicating SARS-CoV-2 has created a challenge for antimicrobial stewardship. Following the introduction of national antibiotic recommendations for suspected bacterial respiratory tract infections complicating COVID-19, a point prevalence survey of prescribing was conducted across acute hospitals in Scotland. Patients in designated COVID-19 units were included, and demographic, clinical and antimicrobial data were collected from 15 hospitals on a single day between 20th and 30th April 2020. Comparisons were made between SARS-CoV-2 positive and negative patients and patients in non-critical care and critical care units. Factors associated with antibiotic prescribing in SARS-CoV-2 positive patients were examined using Univariable and multivariable regression analyses. A relatively low prevalence of antibiotic prescribing in SARS-CoV-2 hospitalised patients and a low proportion of broad-spectrum antibiotics in non-critical care settings were observed, potentially reflecting national antimicrobial stewardship initiatives. Broad-spectrum antibiotic and antifungal prescribing in critical care units were observed, indicating the importance of infection prevention and control and stewardship initiatives in this setting (Khor et al., 2020).

Prior to the pandemic, active learning activities showed promising results. For example, we found a study conducted across the US hospitals that applied educational activities and webinars that encouraged collaboration with the clinical microbiology laboratory, integrating nurses into stewardship activities and antibiotic allergies. This AMS educational program entitled ‘Building Stewardship: A Team Approach Enhancing Antibiotic Stewardship in Acute Care Hospitals’ offered by the Agency for Healthcare Research and Quality (AHRQ) safety program was highly effective, as it focused on the importance of Antimicrobial Stewardship Programs (ASP), strategies for implementation, and operational issues, including an understanding of pharmacodynamics, business models, and electronic surveillance (Mehta et al., 2014). The AHRQ educational components were also used in another study in an innovative and easy way, such as 1-page documents and accompanying user guides on infectious disease syndromes. The document could be used as (1) informational attractive display posters, (2) discussion points on clinical rounds, or (3) an outline for developing local guidelines (Tamma et al., 2021). However, during the pandemic, AMS education was found in only one study and showed an essential impact. There was a critical need for structured AMS education to deal effectively with any emergency/crisis (Ashiru-Oredope et al., 2021).

‘Computer Decision Support’, ‘Surveillance’, and ‘Antibiotic Order Form’ strategies were found only in two studies PP. However, only ‘Computer Decision Support’ and ‘Surveillance’ were found in one study DP (Ashiru-Oredope et al., 2021). During the pandemic, the use of technology has had a significant impact on AMS implementation. Positive outcomes of COVID-19 on AMS
activities included: technology being increasingly used as a tool to facilitate stewardship, e.g., virtual meetings and ward rounds.

The use of hospital electronic prescribing systems facilitated AMS activities by antimicrobial pharmacists. There was a UK-wide decrease in audit activities undertaken by antimicrobial pharmacists. Additionally, PHE Fingertips data support the suspicion of increased ‘just in case’ prescribing of antimicrobials was decreased DP. The national surveillance database indicated a substantial increase in antibiotic prescribing (DDD/1000 admissions) during the COVID-19 period (Ashiru-Oredope et al., 2021). The use of integrated computerised systems was still effective in reducing AMR. Interestingly, the use of new technology ideas, such as mobile applications in updating the antimicrobial guidelines was effective, such as the Commonwealth Partnerships for Antimicrobial Stewardship (CwPAMS) App (Ashiru-Oredope et al., 2021), antibiotic order forms, prescribing and availability of guidelines on smartphones (Nampoothiri et al., 2021).

Laboratory surveillance and feedback were found in 46% of the included studies. The surveillance of antimicrobial use and resistance has been used as a crucial part of AMS implementation, especially when accompanied by other strategies, such as antibiotic restriction, as shown in the study conducted in Germany. The formulary restriction of specific antibiotics (e.g., tigecycline and colistin), the creation of selective antibiotic resistogram profiles, the implementation and electronic access to antimicrobial prescribing guidelines, and mobile applications were used as AMS toolkit PP Surat et al., 2021. laboratory results and microbiology were essential data sources in AMS implementation (Mehta et al., 2014). During the pandemic, reviewing the patient’s laboratory data was also an integral part of the patient’s clinical examination by the ID specialist or ID fellow. It is also accompanied by a review of the patient’s laboratory data, all prescribed antimicrobials, and a subsequent daily, rounding-based, in-person approach to feedback by the ID doctors. Additionally, it was used in AMS case-based education (Spernovasilis et al., 2021).

**Antimicrobial stewardship measures and quality improvement**

As mentioned in the result section, there should be measures/metrics to manage AMS implementation properly. This could be conducted by identifying the measures that can be used to evaluate the outcome of AMS implementation to improve antibiotic use and AMS intervention strategies. These measures or metrics can be used for many purposes, such as quality assurance, improvement, comparisons, and benchmarking. Measuring AMS can be divided into four categories: antimicrobial consumption, process measures, outcome measures, and financial (Department for Health and Wellbeing, 2019). The AMS strategies have significant value with beneficial clinical, resistance and economic impact(s) (bioMérieux Website, 2019) (Table 3.6) (Figure 3.1). For more details, see Appendix 25.
Monitoring trends in antimicrobial use and resistance within a hospital over several years and also identifying small changes in a single ward over a one-month period are essential to adapting empiric treatment according to local resistance trends, demonstrating changes in practice over time and identifying wards with high antimicrobial usage or use of non-policy antimicrobials and define targeted interventions required (BSAC, 2019). Surveillance of antimicrobial use and resistance is important either at the hospital, local, regional, and national levels, such as in the UK (WHO, 2022), Wales (ECDC, 2022), Sweden (Choi et al., 2021), Australia (WHO, 2018), and Canada (PHE, 2018) and at the global level, such as WHO (Patel et al., 2020) and ECDC (WHO, 2009).

Quality improvement and indicators were the most commonly used measures among the included studies, as found in about 83% of the included studies. However, quality improvement projects were found in two studies during the COVID-19 pandemic (Ashiru-Oredope et al., 2021; Williams et al., 2021). It could be used at any stage of the antibiotic use process. The quality improvement activity assists clinicians in selecting the appropriate antibiotic, dose, duration, and route of administration to optimise clinical outcomes while minimising the selection of pathogenic organisms and the emergence of resistance. Importantly, there was an increasing linkage between ASPs and 146 hospital patient safety and quality initiatives. Interestingly, it was essential to follow up and monitor results using appropriate quality improvement committees (Trivedi et al., 2013).

A single-centre quality improvement study with a retrospective evaluation of the impact of antimicrobial stewardship measures on optimising antibacterial use in intra-abdominal infections requiring emergency surgery was performed (Surat et al., 2021). The use of the performance of a PPS to provide feedback on validated quality indicators (QIs) for appropriate antibiotic use (PPS-QI) demonstrated a reduction in geometric mean LOS of 0.8 days in the multicentre cluster-randomized clinical trial to improve antibiotic use and reduce the length of stay in hospitals in the Netherlands (Kallen et al., 2021). Quality improvement activities, such as national quality improvement schemes, were one of the AMS measures that were negatively impacted by the COVID-19 pandemic (Ashiru-Oredope et al., 2021). It could also be used to measure the improvement of AMS activities, such as the use of PCT-based guidelines as a useful tool for rationalising the use of antibiotics in patients with COVID-19 (Williams et al., 2021).

The presence of ongoing AMS quality indicators is one of the essential factors in maintaining preparedness for any emergency or crisis, especially at the national level (ESPAUR, 2022). During the Pandemic, an interesting study was conducted at Sheffield Teaching Hospitals NHS Foundation Trust (STHNFT). This study aimed to evaluate the effectiveness of the implemented guideline, which recommended that antibiotics can be withheld in patients with COVID-19 with PCT <0.25 ng/mL unless felt necessary by a senior clinician. Additionally, the PCT in an electronic 'COVID order set' facilitated AMS measures and surveillance were included. This study found that a PCT-based guideline can be a useful tool for rationalising the use of antibiotics in patients with COVID-19 (Williams et al., 2021).
Both LOS and Cost were found in three studies, only PP. The use of LOS had several advantages: it was easy to measure, could be applied to all admitted patients, reflected the recovery time of hospitalised patients and drove hospital costs (Kallen et al., 2021). LOS was used to examine the antimicrobial use and LOS before and after a change in AMS approach at the Hospital of the University of Pennsylvania, a 776-bed tertiary care academic medical centre in Philadelphia and showed a significant increase after the change in AMS strategy from Pre-authorization and Prospective Audit with Feedback (Mehta et al., 2014). Interestingly, when prior to authorisation, AMS strategy was conducted in costly antibiotics, such as including aztreonam, ceftazidime, daptomycin, levofloxacin, linezolid, and meropenem) and showed a promising outcome in decreasing the LOS and cost. LOS is an important factor in healthcare cost analysis. Based on the national health insurance claims database and specific health check-ups in Japan, the appropriate use of antibiotics and AMS implementation was paramount (Moriyama et al., 2021).

Before 2019, there were no reliable means for measuring antimicrobial usage. The WHO promoted measurable tools, such as the DDD and DOT, to allow comparisons for antimicrobial usage among hospitals and countries (WHO, 2009; ReAct, 2017). In the included studies, the DDD and DOT are the most common AMS measures, as they were used in 53% of PP and 28% of DP. Significantly, we found another study promoted the use of KPIs, such as the AMR local indicators - produced by the UKHSA among the National Health Service (NHS) hospitals in England, and it showed a significant outcome in AMS and provided a comparative measure for the antibiotic prescribing among different periods DP (Ashiru-Oredope et al., 2021; WHO, 2019).

On the other hand, the CDI rate was used to measure the outcome of AMS implementation (Trivedi et al., 2013). It was found that a reduction in antibiotic use and hospital-onset CDI rates was an outcome of implementing the Agency for Healthcare Research and Quality Safety Program across US hospitals (Tamma et al., 2021). During the pandemic, there was a concern about increasing CDI rates as a result of the COVID-19 pandemic across all NHS acute trusts in England (Ashiru-Oredope et al., 2021). Interestingly, data on CDI was collected as a contribution to AMS activities DP (Williams et al., 2021).

A study published in Cambridge University Press aimed to develop and implement antibiotic stewardship activities in urgent care targeting non-antibiotic antibiotic-appropriate acute respiratory tract infections (ARIs). The AMS activities were started in fiscal 2020 and included measure development, comparative feedback, and clinician and patient education. This study measured antibiotic prescribing in fiscal years 2019, 2020, and 2021 for the stewardship targets, potential diagnosis-shifting visits, and overall. Additionally, it collected patient satisfaction data for ARI visits. The antibiotic prescribing rate decreased for stewardship-measure visits from 34% in FY19 to 12% in FY21. Although AMS was affected by the COVID-19 pandemic, an ambulatory antimicrobial stewardship program that focused on improving non-antibiotic-appropriate ARI prescribing was associated with decreased prescribing for (1) the stewardship target, (2) a diagnosis-shifting measure, and (3) overall antibiotic prescribing (Public Health Wales, 2018).
Phase 2: Retrospective Medical Records Review

Start Smart, Then Focus: Antimicrobial Stewardship Before and During the COVID-19 Pandemic at a Secondary Care

This study has been published in Frontier, Microbiology: https://www.frontiersin.org/articles/10.3389/fmicb.2023.1298858/full.


This retrospective study evaluated the clinical and demographic characteristics of patients admitted to Bedfordshire Hospitals NHS Foundation Trust with RTIs during both PP and DP periods. The results revealed that most clinical and demographic characteristics were not significantly different between the two periods, except for admission speciality and gender. The shift in the gender distribution of patients and the changes in admission specialities could be attributed to various factors, including the impact of COVID-19 on the healthcare system, patient demographics, and behavioural changes in healthcare-seeking patterns during the pandemic. The COVID-19 pandemic significantly influenced the number of patients admitted with RTIs. An increase in admissions in December 2019 could be attributed to the rapid spread of COVID-19 and its impact on respiratory health. A subsequent decline in March 2020 and June 2020 coincided with public health measures and the second national lockdown (ESPAUR, 2021). Other factors affecting initial antibiotic prescribing, including patient age, allergies, diagnosis, and comorbidities. The age group with the highest number of admissions in both years was 75-84, consistent with the well-established notion that older adults are more susceptible to respiratory infections and often require hospitalisation. This finding highlights the importance of focusing on preventive strategies and optimising care for this vulnerable population. The classification of age groups and gender revealed interesting differences between the two periods. While the majority of admissions in 2019 were females aged between 75-84, the highest number of admissions in 2020 involved males aged 75-48. This shift in the gender distribution might be attributed to the differential impact of COVID-19 on males and females. Regarding the length of stay (LOS), there were no significant differences in the average LOS between 2019 and 2020. However, the maximum LOS decreased from 119 days in 2019 to 97 days in 2020, which might indicate changes in hospital policies and resource allocation during the pandemic. The healthcare system faced unprecedented challenges due to the COVID-19 pandemic, and hospitals were compelled to adapt their practices to
accommodate the increased demand for beds and resources. This could have influenced the observed reduction in maximum LOS during the pandemic.

**Phase 3: Prospective Survey Study**

Healthcare professionals’ knowledge, attitudes and perceptions regarding antibiotic prescribing, antibiotic resistance and stewardship during the COVID-19 pandemic: A descriptive study at a secondary care setting in the UK

This survey questionnaire was conducted in one English NHS Foundation Trust and focuses on assessing HCPs’ KAP towards antibiotic prescribing, AMR, and AMS during the COVID-19 pandemic. The study participants demonstrated good knowledge and practice; however, their attitude requires further improvement. Such findings highlight a deficiency in efficacious AMS educational and training programmes. Furthermore, this study identified certain HCPs who need to improve their knowledge and practice towards antibiotic prescribing, especially during the pandemic. The study provides vital insights into HCPs’ knowledge and perceptions concerning antibiotic prescribing, AMR, and AMS during the COVID-19 pandemic, with a median knowledge score of 50.13%. Recently, a Saudi Arabian study reported a median knowledge score of 72.73% among primary healthcare workers on antibiotic use, contrasting with Pakistani clinicians in Lahore’s public hospitals, who displayed significant knowledge gaps in AMR and AMS. Despite recognizing AMR as a global issue, many lacked understandings of appropriate antibiotic selection, with a call for more education highlighted.

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Five Rights of Antibiotic Safety: Antimicrobial Stewardship at One NHS Foundation Trust in England Before and During the COVID-19 Pandemic:

Start Smart, Then Focus: Antimicrobial Stewardship Practice at One NHS Foundation Trust in England Before and During the COVID-19 Pandemic:
https://www.medrxiv.org/content/10.1101/2023.06.09.23291146v1

Parent publications

Results of Three-Phase Research Project Investigating Antibiotic Prescribing and Antimicrobial Stewardship in 2019 and 2020

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