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A Retrospective Surveillance of the Antibiotics Prophylactic Use of Surgical Procedures in Private Hospitals in Indonesia

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Abstract

Background: According to international guidelines, prophylactic antibiotics in elective surgery should be given as a single dose 30 to 60 minutes before the operation is conducted. Postoperative administration of antibiotics should be discontinued 24 hours after surgery to minimize bacterial resistance and to keep control over hospitalization costs. There is a lack of data on the actual antibiotic use around surgical procedures in Indonesia. **Objective:** This retrospective surveillance study aimed to obtain defined daily doses (DDD) and DDDs per 100 bed days (DDD-100BD) for prophylactically used antibiotics in two private hospitals in Surabaya, East Java. These hospitals are considered to be representative for the current situation in Indonesia. **Method:** Data from a total of 693 patients over a nearly 1-year period (2016) were collected and evaluated. **Results:** The overall DDD per patient was 1.5 for hospital A and 1.7 for hospital B. The overall DDD-100BD was 30 for hospital B. Of the 24 antibiotics given prophylactically, ceftriaxone was the most commonly used in both hospitals. **Conclusion:** There was a clear discrepancy between daily practice in both hospitals and the recommendations in the guidelines. This study shows that better adherence to antibiotic stewardship is needed in Indonesia. Substantial improvements need to be made toward guided precision therapy regarding quantity (dose and frequency), route of administration (prolonged intravenous), and choice of the type of antibiotic.

Keywords

defined daily doses (DDD), DDD per 100 bed days (DDD-100BD), antibiotic prophylaxis, operating theater, antibiotic resistance

The Impact on Practice

This study will encourage the hospital management to do better antibiotic stewardship program, rational antibiotic use, and prevent bacterial resistant occurrence infection for the patient.

Introduction

Antibiotic prophylaxis is defined as the use of antibiotics before, during, and after a surgical procedure to prevent infections, and is common practice in and around operating theaters. Antibiotic prophylaxis should, however, be applied carefully. Excessive use as well as the application of broad spectrum antibiotics harbor a serious risk of resistance development. Examples are the emergence of methicillin-resistant *Staphylococcus aureus* (MRSA) bacteria and of hypervirulent strains such as *Clostridium difficile*, which is a growing cause of antibiotic-associated colitis.[1,2]

The World Health Organization (WHO) has published a surveillance report on antimicrobial resistance at a global scale, from which it becomes clear that data on the incidence of antibiotic resistance in Indonesia are very scarce. A more general picture for the South East Asian area has been generated in projects of the Asian Network for Surveillance of Resistant Pathogens (ANSORP) and in the Gonococcal Antimicrobial Surveillance Programme (GASP).[3] A systematic review shows that the only article about antibiotic stewardship in Indonesia is the Antimicrobial Resistance in Indonesia (AMRIN) study.[4]

To stimulate responsible prophylactic use of antibiotics, various guidelines exist. On an international level, there are "Clinical Practice Guidelines for Antimicrobial Prophylaxis in Surgery" and "Antibiotic Prophylaxis in Surgery"[5,6]; the

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only general national guideline is from the Indonesian Ministry of Health (IMOH): *Pedoman Umum Penggunaan Antibiotik* (National Guideline for Antibiotic Use in Indonesia).[7] Some hospitals in Indonesia use additional guidelines. The Regional Public Hospital Dr. Soetomo in Surabaya, a referral hospital for East Indonesia and a large tertiary care hospital with more than 1200 beds serving as a referral hospital for any type of patient from Eastern Indonesia, uses the guideline *Pedoman Penggunaan Antibiotika Di Bidang Bedah* (Antibiotic Use Guideline in the Operating Theatre).[8] Hospitals without own antibiotic use guideline usually use the one from the IMOH or an international guideline, but in Surabaya, the guideline from the Regional Public Hospital is used as a reference as well.

Antibiotic prophylaxis is applied whenever the costs and the morbidity associated with infection are higher than the costs and the morbidity associated with the prophylaxis. Factors relating to surgical site infections or to consequences of infection comprise the surgical procedure (including infection-control strategies), the surgeon's experience and technique, the duration of the procedure, and patient-related factors (including the underlying medical condition). The choice for a prophylactic antibiotic should be based on the pathogens relating to a specific surgical procedure. Specific antibiotics are used for certain conditions, that is, cefepime is used for lung transplant recipients without known colonization; meropenem is used for complicated skin and skin structure infections or complicated intra-abdominal infections; and amikacin plus metronidazole are used for colorectal surgery. Broader spectrum antibiotics, that is, fourth-generation cephalosporins (cefepime, cefpirome), carbapenems (meropenem, imipenem/cilastatin), and some aminoglycosides (kanamycin, amikacin), should be used restrictively.[5,6]

In Indonesia, the prescribing adherence to the guidelines has been reported to be poor. Only 6.1% of the antibiotics used in orthopedic surgery in Dr. Mintohardjo Navy Hospital, a general tertiary care hospital in Jakarta, are included in the IMOH's guideline. The same counts for the use of antibiotics for clean-contaminated wounds in surgery in a district tertiary care hospital in Jakarta with 21.5%. The most frequently used antibiotic prophylaxis in both hospitals was ceftriaxone (87.8% and 49.8%, respectively).[9-11] Ceftriaxone also happened to be the most frequently used antibiotic for prophylaxis in appendicitis surgery in 25 patients in the Haji General Hospital Surabaya, Indonesia.[12] Data so far available on the prophylactic use of antibiotics in Indonesia are limited. The reports lack information on providing units of antibiotics as defined daily dose (DDD) and refer to only a small number of patients.

The current retrospective study aims to provide more comprehensive information on the prophylactic antibiotic use around surgical procedures in Indonesian hospitals to allow a better comparison worldwide. The study covers nearly 1 year of medical records (2016) of two tertiary care private hospitals in Surabaya. The antibiotic use in these two hospitals is considered to be representative for Indonesia.

Aim of the Study

The aim of this study was to obtain DDD and DDDs per 100 bed days (DDD-100BD) for prophylactically used antibiotics in the hospital.

Ethics Approval

For this type of study, formal consent is not required. This article does not contain any studies with human participants performed by any of the authors; no active intervention was introduced. The study has approval from the hospital management and applies Indonesian Law for the Protection of Personal Data and the Declaration of Helsinki. The study has approval from the university and the students have the foreign research permit from the Ministry of Research, Technology, and Higher Education.

Methods

Study Design

A retrospective study was conducted by extracting data from two tertiary care private hospitals (A and B), in Surabaya, Indonesia. Hospital A has 201 beds and 5 operating theaters, whereas hospital B has 324 beds and 10 operating theaters. Patient files covering the period from January 1, 2016, to October 24, 2016 (hospital A), and from January 2, 2016, to November 22, 2016 (hospital B) were used for the study. Patient ID, gender, age, and the type of surgery were already included in the digitalized files while all medication data, such as type, dose, date, and time of administration, were recorded on the medication chart as part of the patient's medical record. In total, data of 693 patient charts were reviewed from both hospitals, categorized, and descriptively analyzed. At the time this study was conducted, an Antibiotic Stewardship Program was not established at either hospital A or B.

The type of surgery was categorized into one of the following six groups: (1) caesarean delivery, orthopedic other than clean orthopedic surgery, and vascular surgery; (2) laparoscopy and laparotomy; (3) appendectomy; (4) head surgeries; (5) clean orthopedic surgery; and (6) other (including all types of surgery that do not fit in one of the five other groups, that is, anal fistulectomy, hernia repair, mastectomy, thyroidectomy, tonsillectomy, ureterotomy, etc.). The antibiotics were classified into 14 groups, according to the Anatomical Therapeutic Chemical (ATC) classification for antibacterials for systemic use (J01).[13]

Data about antibiotic use were divided into five categories according to the quantity used during patient stay, namely, (1) no antibiotic, (2) 1 antibiotic, (3) 2 antibiotics, (4) 3 antibiotics, and (5) more than 3 antibiotics. No antibiotic means

Table 1. Grouped Surgery Distribution Per Hospital in 2016.

Grouped surgery	Hospital A (number, % of total A)	Hospital B (number, % of total B)	Total (number, % of total A + B)
Caesarean delivery, other orthopedic, vascular	167 (47.8)	74 (21.6)	241 (34.8)
Laparoscopy and laparotomy	38 (10.9)	10 (2.9)	48 (6.9)
Head surgeries[a]	28 (8.0)	22 (6.4)	50 (7.2)
Clean orthopedic	10 (2.9)	34 (9.9)	44 (6.3)
Appendectomy	7 (2.0)	32 (9.3)	39 (5.6)
Other[b]	100 (28.6)	171 (49.9)	271 (39.1)
Total	350	343	693

[a]Except clean head procedures.
[b]For example, anal fistulectomy, hernia repair, mastectomy, thyroidectomy, tonsillectomy, ureterotomy.

that a patient received no prophylactic antibiotic at all; 1 antibiotic means patients received only one regimen of antibiotic prophylaxis; 2 antibiotics means patients received 1 antibiotic prophylaxis and 1 additional antibiotic; 3 antibiotics means patients received 1 antibiotic prophylaxis and 2 additional antibiotics; and more than 3 antibiotics means patients received 1 antibiotic prophylaxis and more than 2 additional antibiotics.

Data Analysis

Antibiotics use was expressed as DDD and DDD-100BD. The DDD is a drug utilization figure and used for comparison to its WHO's DDD standard. The latter is a unit of measurement of the assumed average maintenance dose per day for a drug used for its main indication in adults. The antibiotic use in hospitals A and B was compared using the total DDD per antibiotic, DDD per patient, and DDD per 100 bed days.[13,14]

The following equations were used for calculations:

$$\text{Total DDD per antibiotic} = (\text{Number of packages used}) \times (\text{Number of DDD in a package})$$

$$\text{DDD per patient} = \frac{\text{Total DDD}}{\text{Number of patients}}$$

$$\text{DDD per100 bed days} = \left(\frac{\text{Total DDD}}{\text{Number of occupied bed days}}\right) \times 100$$

A bed day is defined as a day during which a person occupies a bed (the patient stays overnight in a hospital), approximated by multiplying the number of hospital beds with the bed occupation rate or patient's length of stay.

Results

In the two hospitals included in this study, various kinds of minor and major surgeries are performed as long as the required expertise and facilities are present. Most common in both hospitals is a caesarean delivery, followed by laparoscopic procedures and head surgeries in hospital A, and orthopedic procedures and appendectomy in hospital B. Table 1 gives an overview of all grouped surgical procedures that were carried out during the period of this review.

Both hospitals used more than 20 different antibiotics for the prophylactic surgical site infections during the period covered by this study. Table 2 gives a survey of these antibiotics and the corresponding DDD. Third generation cephalosporins were frequently used in both hospitals, especially ceftriaxone. In hospital A, third generation cephalosporins contributed to 77.1% of the total DDD, in hospital B, 32.3%. Compared to hospital A, in hospital B, substantially more aminoglycosides, fluoroquinolones, and metronidazole were used. The DDD per patient was 1.5 for hospital A and 1.7 for hospital B. The DDD-100BD was 30.4 for hospital B. The number of occupied bed day in hospital A could not be calculated because there was no information on number of beds, bed occupation rate, or length of stay; the total patient's length of stay at hospital B was 1868 days.

In Table 3, the time points of administration and applied administration routes are presented. Antibiotic prophylaxis was given preoperative, perioperative, and postoperative (more than 24 hours after surgery). On average, there was only 1 DDD for each patient preoperative and perioperative and less than 1 for each patient >24 hours postoperative in hospital A. In hospital B, this was less than 1 for each patient preoperative and perioperative and on average 1 for each patient >24 hours postoperative. Approximately 78% of DDD were administered intravenously, while 22% were orally administered (Table 3).

Table 4 shows the number of patients for the treatment regimens applied. Treatment regimens stretch from no antibiotic at all to 5 antibiotics. In both hospitals, 2 or 3 antibiotics was the most common prophylactic treatment. The 6 patients receiving 5 antibiotic regimens (Table 4) were patients of whom the length of stay (9-24 days) was longer

Table 2. Prophylactic Antibiotic Use Around Surgical Procedures in Hospitals A and B, Expressed as DDD.

Antibiotic	Hospital A	Hospital B
Amphenicols		
Thiamphenicol	—	2.5
Penicillins with extended spectrum		
Amoxicillin	0.5	—
Penicillins combined with beta-lactamase inhibitors		
Ampicillin and enzyme inhibitor	7.3	8.7
Amoxicillin and enzyme inhibitor	17.8	44.0
Cephalosporins, first generation		
Cefazolin	7.0	25.5
Cefadroxil	4.1	5.8
Cephalosporins, second generation		
Cefuroxime	27.9	5.2
Cefaclor	0.2	—
Cephalosporins, third generation		
Cefotaxime	6.8	1.6
Ceftazidime	21.3	7.1
Ceftriaxone	285.9	97.8
Ceftizoxime	25.5	0.3
Cefixime	42.5	59.3
Cefoperazone, combinations	10.0	17.3
Cephalosporins, fourth generation		
Cefepime	1.0	12.5
Cefpirome	7.3	0.3
Carbapenems		
Meropenem	28.0	53.0
Imipenem and enzyme inhibitor	—	19.0
Macrolides		
Azithromycin	1.7	0.8
Lincosamides		
Clindamycin	—	3.3
Aminoglycosides		
Gentamicin	0.3	9.9
Kanamycin	—	0.5
Amikacin	1.5	77.3
Fluoroquinolones		
Ciprofloxacin	5.0	18.8
Levofloxacin	5.0	33.5
Imidazole derivatives		
Metronidazole	1.7	63.3
Other antibiotics		
Fosfomycin	0.4	—
Total DDD	508.5	567.0
DDD per patient	1.5	1.7
DDD per 100 bed days	—	30.4

Note. DDD = defined daily doses.

than of the average patient (5.4 days). Their diagnoses were noninsulin-dependent diabetes mellitus with neurological complication, acute peritonitis, rectal cancer, focal brain injury, and benign neoplasm of the ovary.

Discussion

This study clearly shows that the volume of prophylactic antibiotic use is large, with more than 80% using two or more antibiotics, and that a wide variety of different antibiotics including in most cases third generation cephalosporins was applied in the study hospitals.

The choice of an antibiotic should be based on its antibacterial spectrum and the indication. The main bacteria causing surgical site infections after clean procedures are the gram-positive *S. aureus* and coagulase-negative staphylococci (eg, *Staphylococcus epidermidis*) which are common species of the skin flora. In clean-contaminated procedures, including abdominal surgery and heart, kidney, and liver transplantations, bacteria that cause surgical site infections are similar to those at the skin flora in a clean procedure, plus gram-negative rods, and enterococci. According to the guideline published by IMOH[7], cefazolin, a first generation cephalosporin, is applied to prevent such infections. Third generation cephalosporins such as the frequently used ceftriaxone and cefixime in hospitals A and B are not the prophylactic antibiotics of choice here. Cefixime was used as a ceftriaxone substitute when switching from an intravenous to an oral antibiotic. Besides staphylococci and enterococci, ureaplasma and anaerobic bacteria are common organisms isolated from wound infections. Therefore, azithromycin or metronidazole may be added to suppress these organisms. Furthermore, the addition of vancomycin to cefazolin is recommended when MRSA is a frequent cause of infection.[15,16] For patients allergic to beta-lactam, the recommended prophylactic antibiotics are gentamicin, fluoroquinolone, clindamycin, or vancomycin.[6]

Meropenem and amikacin, both frequently applied, especially in hospital B (Table 2), are highly potent broad spectrum antibiotics used as alternatives if the bacteria are already unsusceptible to cephalosporins and gentamicin. Ceftriaxone, amikacin, and meropenem are not recommended for specific gram-positive skin flora. Therefore, the use of ceftriaxone should be limited and only be applied based on results from an antibiotics sensitivity test showing the presence of gram-negative bacteria.

The DDD is used for benchmarking between hospitals.[14] Overall, in this study, the antibiotic use was 30 DDD per 100BD meaning that on average, there were 0.3 WHO's DDD per patient per day or 30 WHO's DDD for 100 patients per day. This means that 30% of the patients received a DDD of a prophylactic antibiotic per day.

The antibiotic use in hospitals A and B in 2016, with higher preference for cephalosporins than for penicillins, was different from the antibiotic use in two other hospitals in Indonesia in 2005,[17] where penicillins were preferred over cephalosporins. Comparable DDD-100BD were reported for the Isparta State Hospital in Turkey in 2013, a secondary health care facility with 372 beds, with 49.1 DDD-100BD; <2 DDD per patient.[18] It was lower than two hospitals in

Table 3. Administration Routes and Time Point of Administration of Prophylactic Antibiotics in Hospital A and B, Expressed as DDD.

	Preoperative and perioperative		>24 hours postoperative		
	Hospital A	Hospital B	Hospital A	Hospital B	Total DDD (%)
Parenteral	291.6	168.1	113.0	264.7	837.4 (77.9)
Oral	24.0	26.8	79.8	107.4	238.0 (22.1)
Total DDD	315.6	194.9	192.8	372.1	1,075.4 (100)

Note. DDD = defined daily doses.

Table 4. Regimens of Prophylactic Antibiotic Therapy Around Surgical Procedures in Hospital A and B.

Hospital/category	No antibiotic (number/ total number, %)	1 antibiotic (number/ total number, %)	2 antibiotics (number/ total number, %)	3 antibiotics (number/ total number, %)	>3 antibiotics (number/ total number, %)
A	62/350 (17.7)	4/350 (1.1)	167/350 (47.7)	111/350 (31.7)	6/350[a] (1.7)
B	21/343 (6.1)	21/343 (6.1)	146/343 (42.6)	133/343 (38.8)	22/343[b] (6.4)

[a]6 patients with 4 antibiotics.
[b]16 patients with 4 antibiotics, 6 patients with 5 antibiotics.

Nablus, Palestine, in 2012, with 110 and 205 beds, that is, more than 100 DDD per 100 bed days; 4 and 6 DDD per patient.[19]

Some patients who underwent elective surgery, and were previously healthy, were given an antibiotic injection before surgery and oral antibiotics in the recovery room till the moment they were discharged (Table 4). Others only received an injection with antibiotic before surgery. The decision of giving oral antibiotics after surgery depends on the patient's condition and surgeon's observation. The route of administration should ensure achievement of the minimum effective drug concentration in blood and tissue during the period the surgical site is open. For many surgical procedures, the preferred route of administration is intravenous.

More than 80% of the patients in both hospitals received one or more additional antibiotics (Table 4). This situation is similar to the situation in 2005 in two governmental teaching hospitals in Indonesia which are almost all (90%) patients in the operating theater used antibiotics.[17] Several patients were given even more than three additional antibiotics during their stay in the hospital. Several studies showed, however, that prolonged antibiotic prophylaxis is not superior or more effective but may elicit bacterial resistance. Amoxicillin-clavulanic acid 1.2 g intravenous twice daily or a single dose of 1 g intravenous ceftriaxone were as effective as 3 times daily intravenous triple antibiotics (ampicillin, gentamicin, metronidazole) for wound infection.[20-24] A review including 16 studies of caesarean sections showed nonsignificant differences between single dose and multiple-dose antibiotic prophylaxis in the incidence of postpartum infectious morbidity, endometritis, and wound infection.[25] A meta-analysis (N = 3808 closed long bone fractures patients) showed that multiple-dose antibiotic prophylaxis was not superior to a single dose.[26]

The choice of antibiotics for prophylaxis in surgery should be one with a narrow bacterial spectrum, tailored to the expected microorganism(s). It is usually given parenterally, and only as a single dose, 30 to 60 minutes before the surgical procedure starts. All other choices or regimens beyond the guidelines are not good practice and should be avoided. The practice in hospitals A and B clearly deviates from the guidelines of antibiotic stewardship. As these hospitals are considered representative for Indonesia, the policy around rational antibiotic prophylaxis should be improved to prevent bacterial resistance development as much as possible.

Limitations

In general, the amount of drugs used in a private hospital in Indonesia will be higher than in a public hospital and may differ from the picture that will be obtained from public hospitals or in a limited resources situation.[27] There are no regulations that may limit the use. A physician in a private hospital simply uses any available antibiotic if deemed necessary for a patient. In a public hospital, most patients are covered by governmental insurance, and therefore, a physician is only allowed to choose an antibiotic from the Indonesian national formulary (Formularium Nasional).[28] This study is limited to only measuring actual prophylactic antibiotic use in operating theater without an evaluation of the appropriateness of antibiotic prophylaxis. Another limitation is the retrospective design of the study. The data were generated from medical records without randomization meaning that differences in antibiotic use between the hospitals can be caused by differences in presence of risk factors.

Conclusion

A fundamental improvement in the use of prophylactic antibiotics in hospitals in Indonesia is required. There is an urgent need for every hospital to publish a guideline of antibiotic use or clinical pathway for every type of surgery, including any complicated surgery and other infectious diseases. Antibiotics should be selected more precisely, dosage and frequency are to be improved, and appropriate route of administration needs to be enhanced. We recommend single dose administration of single narrow spectrum antibiotic within a period of no more than 24 hours for surgical prophylaxis to prevent microbial resistant incidence. Hence, the results of our study are valuable for future policy making in this field. Creating awareness among medical staff, adaptation of antibiotic use policy by the Indonesian government, and continuous monitoring and adjustment to improve will lead to an improved Indonesian health care system with respect to rational prophylactic antibiotic use.

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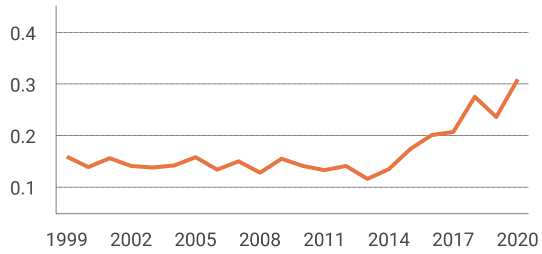

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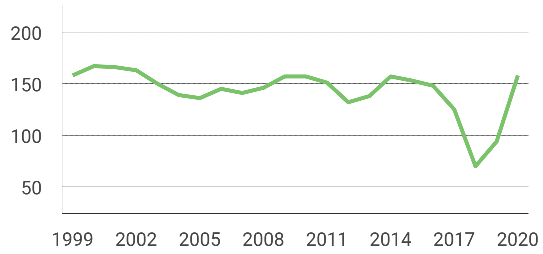

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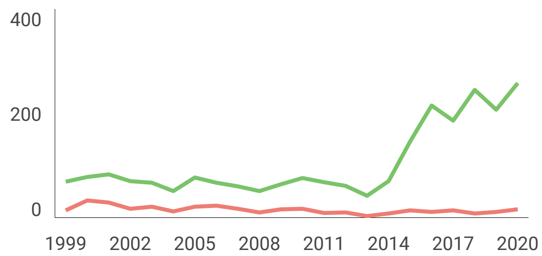

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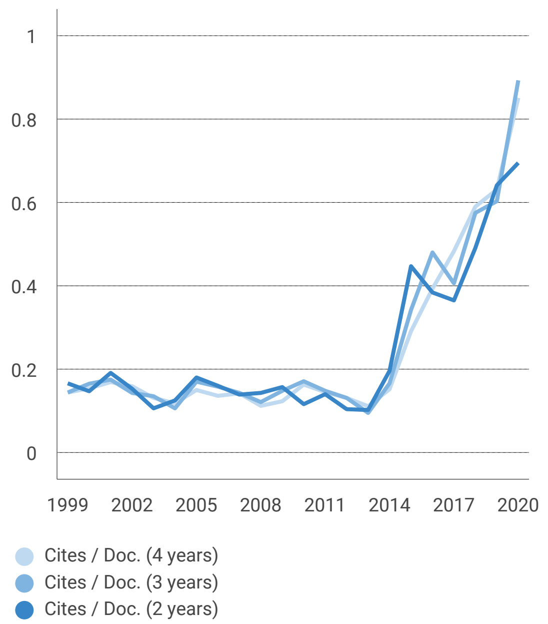

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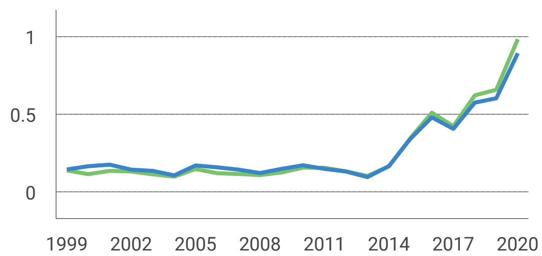

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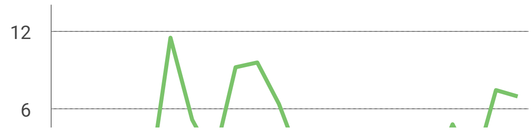

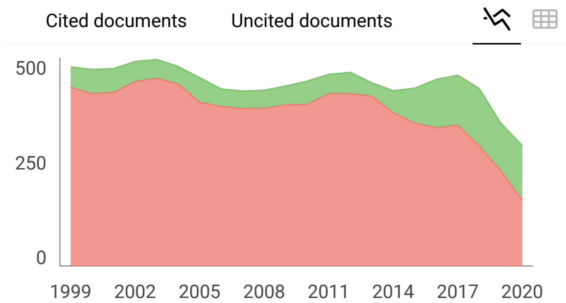

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