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Antimicrobial Resistance Pattern of *Moraxella catarrhalis* and *Haemophilus influenza* in Iran; A Systematic Review

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ABSTRACT

Background: *Haemophilus influenzae* and *Moraxella catarrhalis* are common pathogens in respiratory tract infections, causing some diseases like community-acquired pneumonia, acute sinusitis, and otitis media. Antimicrobial resistance in these pathogens occurs over the years. This systematic review aimed to investigate the antibiotic resistance pattern of these pathogens in Iran in the last 5 years.

Materials & Methods: All original articles related to the antimicrobial resistance of *H. influenza* and *M. catarrhalis* in Iran since 2018 were searched in English and Persian databases. The articles were screened primarily and secondary. After screening the articles (extracted blindly), conflicts were resolved, and the final data were reviewed.

Findings: This study included nine articles after primary and secondary screening steps, comprising 111 *H. influenzae* and 78 *M. catarrhalis* isolates. The lowest resistance of *H. influenzae* isolates was against levofloxacin (0.0%), cefotaxim (11.1%), and ceftriaxone (11.1%), while the highest resistance of these isolates was against tetracycline, co-trimoxazole, and ampicillin. *M. catarrhalis* isolates showed the highest resistance to penicillin (100%), cefazolin (87.5%), cefuroxime (84.4%), ampicillin (84.4%), and amoxicillin (81.2%). Co-trimoxazole resistance rates of *M. catarrhalis* isolates from adenoid tissue and pharynx were different. Resistance to fluoroquinolones was 0.0%; macrolides were the most effective antibiotics.

Conclusion: Fluoroquinolones and macrolides are the most effective antibiotics for *M. catarrhalis*, while fluoroquinolones and cefotaxime or ceftriaxone work best for *H. influenzae*. It is recommended to use fluoroquinolones and macrolides for managing outpatients and fluoroquinolones, macrolides, or ceftriaxone for managing inpatients. Prescription of β-lactams and/or co-trimoxazole is ineffective.

Keywords: *Moraxella Catarrhalis*; *Haemophilus Influenza*; Respiratory Tract Infection; Drug Resistance; Antimicrobial Resistance

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Introduction

Haemophilus influenzae and *Moraxella catarrhalis* are two common microorganisms found in community-acquired pneumonia and other upper and lower respiratory tract infections. These bacteria are Gram-negative and often found in the nasopharynx and oropharynx [1]. The incidence rate of *H. influenza* infection varies in industrial and non-industrial communities.

The prevalence of *H. influenza* type b has decreased throughout the vaccination era, but the predominance of non-typeable strains has increased the incidence of invasive *H. influenza*e [2-4]. *M. catarrhalis* often colonizes healthy infants, especially in the first year of life [2, 3].

The main diseases caused by *H. influenzae* and *M. catarrhalis* are meningitis, bacteremia, community-acquired pneumonia (CAP), septic arthritis, acute otitis media (AOM), acute sinusitis, and exacerbation of chronic obstructive pulmonary disease (COPD) [1, 2, 4]. With the emergence of resistance to some antimicrobials, antibiotic recommendations have changed over the years. According to previous studies, most *M. catarrhalis* isolates carry β-lactamase enzymes and are resistant to penicillin and amoxicillin. Second- and third-generation cephalosporins or β-lactam antibiotics with β-lactamase inhibitors are used in the treatment of some resistant strains of *H. influenzae* and *M. catarrhalis* [2,4]. Empirical treatment is usually required because causative agents are often difficult to identify in clinical settings [5]. Therefore, knowledge of the susceptibility and resistance patterns of each bacterium in local areas plays an important role in treatment.

Objectives: Due to the increasing detection of these organisms in various syndromes, particularly pneumonia and upper respiratory tract infections, and considering the diversity of resistance mechanisms and the lack of enough supporting data for the treatment of patients, we decided to carry out a systematic review to discuss the drug resistance and susceptibility of these pathogens in order to establish a thorough viewpoint for the treatment of suspected infections caused by these etiologies in Iran.

Materials and Methods

This systematic review was carried out using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 (Figure 1) [6], whereby the authors analyzed the available studies related to *H. influenzae* and *M. catarrhalis* and their antibiotic resistance pattern in Iran in the last 5 years. PubMed, Scopus, Web of Science, and Google Scholar databases were searched. In addition, Irandoc and Magiran were searched for articles published in Persian language. Keywords were searched using Boolean operators "OR" and "AND" in order to find a large number of relevant articles limited to Iran since 2018 in the mentioned databases. In the PubMed database, "*Haemophilus influenzae*" [Mesh] OR "*Moraxella catarrhalis*" [Mesh] AND "antibiotic resistance" [Mesh] were searched to find relevant articles. In other databases, "*Haemophilus influenzae*" OR "*Moraxella catarrhalis*" AND "drug resistance" OR "antibiotic resistance" OR "antimicrobial resistance" OR "antibiotic susceptibility" were searched. Google Scholar was used for the first 15 pages of the search results. In addition, the references of the reviewed articles, which were conducted on antibiotic resistance in Iran were reviewed manually to ensure that there were no missing articles. All findings were imported into Rayyan website [7] as a web tool for conducting reviews, and then their titles and abstracts were screened by two reviewers (FH, ShSh) blindly, and conflicts were resolved. All screening steps were performed following the inclusion/exclusion criteria shown in Table 1. This

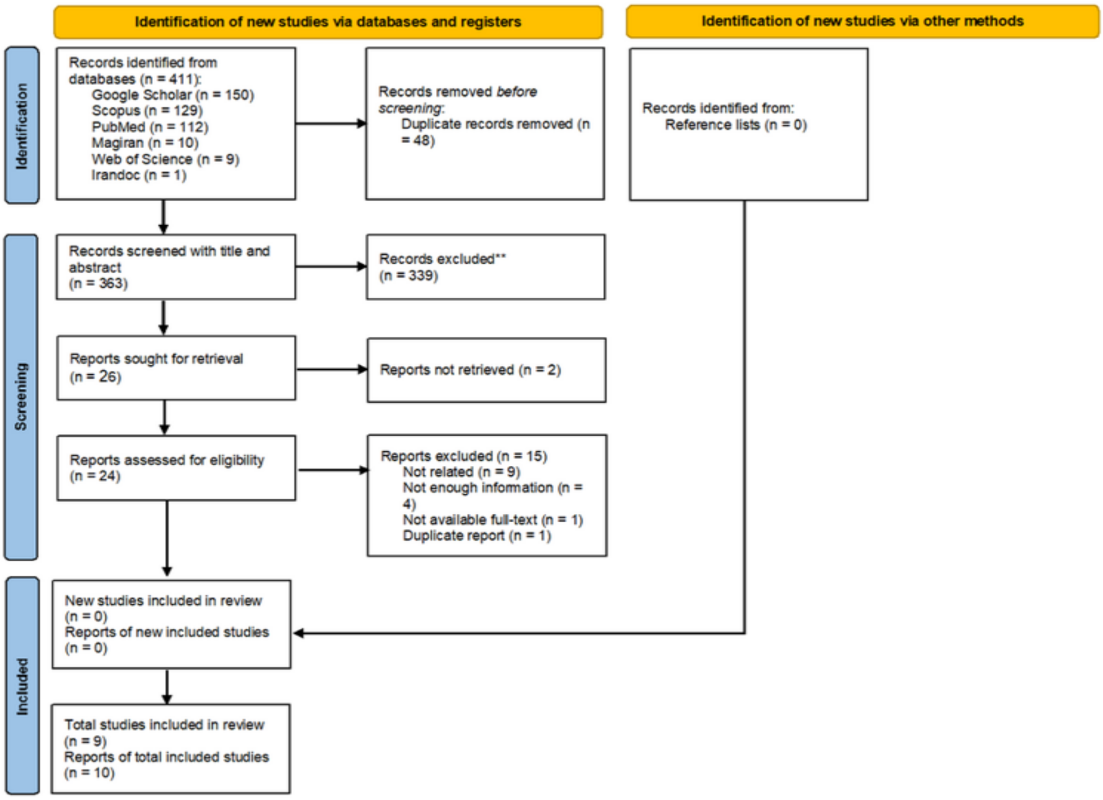

Figure 1) PRISMA flowchart for illustrating the selection of studies

Table 1) Inclusion and exclusion criteria used in the screening steps in this study.

Inclusion Criteria	Exclusion Criteria
All original studies that were not reviews, case reports, or letters	Letters, case reports, case series, reviews, systematic reviews, meta-analysis studies
Studies that included *H. Influenzae* AND/OR *M. Catarrhalis*	Studies that did not include *H. influenzae* AND/OR *M. catarrhhalis*.
Studies that were about drug resistance	Studies that were not about drug resistance
Studies that were conducted in Iran or had Iranian samples	Studies that were not conducted in Iran or had no Iranian samples
Studies that were published since 2018	Studies that were far earlier than 2018

study included original research conducted on drug resistance of *H. influenza* and/or *M. catarrhalis* in the last five years in Iran, and other types of studies or studies about other pathogens were excluded. Primarily-included articles were subjected to full-text analysis, quality assessment was undertaken, and finally included articles were blindly extracted by two other reviewers (HE and AZN), and their conflicts were resolved by another reviewer (HAN).

Findings

By searching keywords, 411 studies were found, of which 48 cases were duplicates. Titles and abstracts of the remaining 363 studies were blindly screened by two reviewers (FH and ShSh), and their conflicts were resolved. Then 24 primarily-included articles were subjected to full-text analysis, of which 15 articles were excluded. Reference lists of previous reviews conducted on antibiotic resistance in Iran were analyzed to ensure that there were no missing relevant articles, but none were found. Eventually, nine articles were included in this study, of which five studies were about *H. influenzae* [8-12], and three studies were about *M. catarrhalis* antibiotic resistance pattern [13-15]. One article was about antibiotic resistance of both *H. influenzae* and *M. catarrhalis* [16]. These articles and their respective samples were the basis for the current study population.

***H. influenzae* findings:** Totally, 152 *H. influenzae* isolates were found in these six studies, of which 111 isolated were studied in terms of their antibiotic resistance pattern. These samples were isolated from nasopharynx (n=73), sinus (n=11), nasolacrimal duct discharge (n=11), sputum (n=7), adenoid tissue (n=6), and cerebrospinal fluid (n=3). All six studies were cross-sectional and used the disc diffusion method (CLSI) for antibiotic resistance testing, except for the study by Eshaghi et al. (2019) [9], which used the polymerase-change reaction (PCR) to detect ROB-1 and TEM-1 genes in isolates, indicating β-lactam resistance. Among the 73 nasopharynx isolates investigated in the study by Shooraj et al. (2019), 90.0% showed resistance to tetracycline. Ciprofloxacin and levofloxacin resistance rates were 0.0%, while 7.8% of the isolates showed intermediate resistance to ciprofloxacin. Resistance rates to co-trimoxazole, ampicillin, chloramphenicol, ceftriaxone, and cefotaxime were 57.7, 43.3, 42.2, 11.1, and 11.1%, respectively. In their study, the minimum inhibitory concentrations (MIC) of ampicillin and chloramphenicole were studied, and ampicillin MIC values of ≤ 1, 2, and ≥ 4 µg/mL were categorized as sensitive, intermediate, and resistant, encompassing 66.7, 5.3, and 28% of the isolates, respectively. Furthermore, chloramphenicol MIC values of ≤ 2 (sensitive), 4 (intermediate), and ≥ 8 (resistant) were associated with 96, 2, and 2% of the isolates, respectively [8]. On the other hand, two isolates from sinus samples were positive for TEM-1 gene, which indicates resistance to β-lactams [9]. Isolates from nasolacrimal duct discharge showed the highest sensitivity to ciprofloxacin and vancomycin [10]. The number of *H. influenzae* strains isolated from sputum, adenoid tissue, and CSF was less than 10; therefor, their results could be different from what actually exists [11, 12, 16]. The included articles are reviewed in detail in Table 2.

***M. catarrhalis* findings:** Totally, 83 *M. catarrhalis* isolates were found in four studies, of which 78 isolates were studied in terms of their antibiotic resistance pattern. The samples were isolated from adenoid tissue (n=33); pharynx, sinus, ear discharge, and pulmonary secretions (n=32); sputum and purulent secretions of the middle ear (n=10); and urine and tracheal aspiration (n=3). All four studies were cross-sectional and used the disc diffusion (CLSI) method for antibiotic resistance testing. Among adenoid tissue samples, 38 isolates were detected (culture: n = 33, PCR: n = 5). These 33 isolates were investigated for antibiotic resistance, the results showed that resistance to co-trimoxazole, rifampicin, erythromycin, ciprofloxacin, and levofloxacin was 94, 36.4, 9, 0.0, and 0.0%, respectively [16]. Also, 32 isolates from pharynx, sinus, ear discharge, and respiratory secretions were resistant to the following antibiotics: penicillins (100%), cefazolin (87.5%), ampicillin and cefuroxime (84.4%), amoxicillin (81.2%), and some other antibiotics listed in Table 3. Among these isolates, resistance to ciprofloxacin, gentamycin, clindamycin, and azithromycin was 0.0% [13]. Isolates from sputum and purulent secretions of the middle ear showed 70% resistance to penicillin, ampicillin, amikacin, gentamicin, chloramphenicol, tetracycline, ciprofloxacin,

Table 2) Review of studies and antibiotic resistance rate of *H. influenzae* (abbreviations: yrs: years, mo: month, CAP: community-acquired pneumonia, CSF: cerebrospinal fluid)

Study Number	Author name	Publication Year	Study type	Sample	Total samples	Number of *H. influenzae*	Antibiotic resistance test	Antibiotics	Resistance rate
1	Shooraj, F et. al. [8]	2019	Cross-sectional	Nasopharynx	328	73	Disc diffusion (CLSI)	Tetracycline Co-trimoxazole Ampicillin Chloramphenicole Ceftriaxone Cefotaxim Ciprofloxacin Levofloxacin	90% (3.3 %) 57.7% (4.45%) 43.3% (31.1%) 42.2% (24.4%) 11.1% (8.9%) 11.1% (10%) 0% (7.8%) 0% (0%)
2	Eshaghi H, et.al. [9]	2019	Cross-sectional	Sinus	137	11	PCR (TEM-1/ROB-1 genes)	β-lactams	18.20%
3	Eslami, F et. al. [10]	2018	Cross-sectional	Nasolacrimal duct discharges	129	11	Disc diffusion (CLSI)	Most sensitive: Ciprofloxacin Vancomycin	26.4% 32.2%
4	Farajzadeh Sheykh, A et.al. [11]	2021	Cross-sectional	Sputum	92	7	Disc diffusion (CLSI)	Amoxicillin/ clavulanate Ciprofloxacin Co-trimoxazole Clarithromycin Ceftriaxone	85.7% 57.1% 42.9% 28.6% 28.6%
5	Sabz,G et. al. [12]	2020	Cross-sectional	Adenoid tissue	200	6	Disc diffusion (CLSI)	Co-trimoxazole Rifampicin Erythromycin Ciprofloxacin Levofloxacin	0% 0% 0% 0% 0%
6	Nahal, H et.al. [13]	2019	Cross-sectional	CSF	89	3	Disc diffusion (CLSI)	Ciprofloxacin ampicillin Co-trimoxazole Tetracycline Ceftriaxone Azithromycin Chloramphenicol	100% 66.6% 66.6% 33.3% 0.0% 0.0% 0.0%

cefazolin, and ceftazidime. Moreover, 0.0% of these isolates were resistant to amoxicillin/clavulanate, azithromycin, erythromycin, and clarithromycin. Resistance to co-trimoxazole was moderate [14]. However, the number of these isolates was 10, which were less than the strains isolated from other clinical samples mentioned above [13, 16]. The included articles are reviewed in detail in Table 3.

Discussion

This review aimed to look at the antibiotic resistance pattern of *H. influenzae* and *M. catarrhalis* in Iran in the last 5 years.

Table 3) Review of studies and antibiotic resistance rate of *M. catarrhalis* (abbreviations: yrs: years, mo: month, AOM: acute otitis media, CSF: cerebrospinal fluid).

Study Number	Author name [reference]	Publication Year	Study type	Sample	Total samples	Number of *M. catarrhalis*	Antibiotic resistance test	Antibiotics	Resistance rate
1	Sabz G, et. al. [12]	2020	Cross-sectional	Adenoid Tissue	200	33	Disc diffusion (CLSI)	Co-trimoxazole Rifampicin Erythromycin Ciprofloxacin Levofloxacin	94% 36.4% 9% 0.0% 0.0%
2	Eghbali M, et. al. [14]	2020	Cross-sectional	Pharynx, sinus Ear discharge, Pulmonary secretions,	400	32	Disc diffusion (CLSI)	Penicillins Cefazolin Ampicillin Cefuroxime Amoxicillin Chloramphenicol Co-trimoxazole Amoxicillin/clavulanate Ceftriaxone Erythromycin Cefepime Tetracycline Gentamycin Ciprofloxacin Clindamycin Azithromycin	100% 87.5% 84.4% 84.4% 81.2% 40.6% 9.4% 6.2% 6.2% 6.2% 3.1% 3.1 % 0.0% 0.0% 0.0% 0.0%
3	Shafiei M, et. al. [15]	2020	Cross-sectional	Sputum Oral and laryngeal pharynx purulent secretions of the middle ear	137	10	Disc diffusion (CLSI)	Penicillin Ampicillin Amikacin Gentamicin Chloramphenicol Tetracycline Ciprofloxacin Cefazolin Ceftazidime Co-trimoxazole Amoxicillin/clavulanic acid Azithromycin Erythromycin Clarithromycin	70% 70% 70% 70% 70% 70% 70% 70% 70% moderate 0.0% 0.0% 0.0% 0.0%
4	Nouri F, et. al. [16]	2020	Cross-sectional	Urine CSF Tracheal aspiration	1998	3	Disc diffusion (CLSI)	Cefepime Gentamicin Amikacin Sulbactam Co-trimoxazole nitrofurantoin cefotetan ceftriaxone levofloxacin cefazolin imipenem meropenem piperacillin/tazobactam ofloxacin vancomycin	resistant

Since *H. influenzae* and *M. catarrhalis* are pathogenic agents in serious conditions such as pneumonia, meningitis, bacteremia, septic arthritis, acute otitis media, and acute sinusitis, it is necessary to know the effective treatment regimens and antibiotic resistance patterns of these species [1, 2, 4]. Totally, 111 *H. influenzae* isolates and 78 *M. catarrhalis* isolates were reviewed. Levofloxacin, ciprofloxacin, and macrolides were the most effective antibiotics for both pathogens, especially *M. catarrhalis*, in most reviewed studies, while there was no study with a large number of *H. influenzae* isolates to compare the effectiveness of fluoroquinolones and macrolides in the case of *H. influenzae* [8, 10, 12, 13, 16]. Ceftriaxone, cefotaxime, and vancomycin were shown to be effective for *H. influenzae*; however, the isolates were less sensitive to these antibiotics than to fluoroquinolones [8, 10]. In the case of *M. catarrhalis*, it was shown that the strains were resistant to cephalosporins, except ceftriaxone and cefepime, to which only 6.2% and 3.1% of the isolates were resistant, respectively [13-15]. Clindamycin and tetracycline were more effective for *M.catarrhalis* compared to *H. influenzae* [8, 13]. Antibiotics to which both pathogens were resistant included chloramphenicol, co-trimoxazole, and β-lactams ascendingly [8, 13, 14, 16]. Amoxicillin-clavulanate was effective for *M. catarrhalis* (6.2% resistant), but there was no study with a large number of *H. influenzae* isolates to investigate amoxicillin-clavulanate resistance rate [11, 13, 14]. Finally, fluoroquinolones were the most effective antibiotics for the treatment of *H. influenzae* and *M. catarrhalis* in the reviewed studies. Table 4 summaries these findings with the descending rate of antibiotic effectiveness in the treatment of *H. influenzae* and *M. catarrhalis*. Co-trimoxazole resistance was 94% in *M. catarrhalis* isolates from adenoid tissue and 9.4% in isolates from pharynx, sinus, and ear discharge. This difference was notable, and its reason needs to be clarified. This difference indicates that isolates from adenoid tissue are more resistant to co-trimoxazole. Adenoid tissue sampling was done from child patients, while other samples were collected from adult patients [13,16]. It could be concluded that *M. catarrhalis* pathogens in children are more resistant to co-trimoxazole than those in adults. In order to confirm this finding, case-control studies with more isolates are needed.

Table 4) Antibiotic sensitivity of *H. influenzae* and *M. catarrhalis*

H. influenzae	*M. catarrhalis*
Flouroquinolones	Flouroquinolones
cefotaxime	Macrolides
ceftriaxone	Clindamycin, Tetracycline
Macrolides	Amoxicillin/clavulanate
Vancomycin	Cefepime
Chloramphenicole	Ceftriaxone
Ampicillin	Rifampicin
Co-trimoxazole	Chloramphenicole
Tetracyclin	Co-trimoxazole
-	Other Cephalosporins
-	Aminoglycosides
-	Amoxicillin, Ampicillin
-	Penicillins

In 2019, Vaez et al. published a meta-analysis about antibiotic resistance of *H. influenza* isolates in Iran up to 2018 [17]. They found that these isolates were resistant to the following antibiotics: penicillin (82.6%), amoxicillin (66.6%), ampicillin (54.8%), co-trimoxazole (53%), tetracyclin (46.7%), erythromycin (40.3%), ceftriaxone (33.1%), ciprofloxacin (30.8%), chloramphenicole (27.7%), and azithromycin (17.4%). In their study, the highest antibiotic resistance was against penicillin, and the most effective antibiotic was azithromycin, while in the current study, the highest antibiotic resistance was against tetracycline, and the most effective antibiotics were fluoroquinolones. Resistance to co-trimoxazole was moderate, similar to the current study results.

Kılıç et al. (2017) conducted a study in Turkey and showed that resistance of *H. influenzae* isolates to co-trimoxazole, ampicillin, amoxicillin/clavulanate, cefotaxime, lefovloxacin was 22.8, 4.3, 1.1, 0.0, and 0.0%, respectively [18]. In the present study, levofloxacin was introduced as the most effective antibiotic against *H. influenza,* but the rate of resistance to ampicillin was higher compared to the Kılıç's study. In the present study, resistance to ampicillin was higher than to co-trimoxazole.

Mather et al. (2019) conducted a systematic review and meta-analysis about antimicrobial resistance in children with acute otitis media [19]. They demonstrated antibiotic resistance pattern of *Streptococcus pneumonia*, *H. influenzae,* and *M. catarrhalis* strains isolated from acute otitis media patients. They found that resistance of *H. influenzae* and *M. catarrhalis* to β-lactams was the highest. The present study indicated that β-lactams were the least effective antibiotics against *M. catarrhalis*, while tetracycline was the least effective antibiotic against *H. influenzae.*

Limitations: This systematic review aimed to look at antibiotic resistance of *H. influenzae* and *M. catarrhalis* in Iran in the last 5 years. The most important limitation of this study was the small number of eligible studies included. Restriction of the search method to "Iran" and "last 5 years" (since 2018) played a significant role in this limitation. In addition, it seems that most researchers in recent years have been interested in researching COVID-19. Therefore, it is notable that recently the number of studies on other pathogens has decreased significantly. However, in this research, all studies related to antibiotic resistance of *H. influenzae* and *M. catarrhalis* in Iran were reviewed to ensure that there were no missing data. Eventually, useful information was obtained regarding the treatment of disorders caused by *H. influenzae* and *M. catarrhalis* pathogens.

Conclusion

In conclusion, fluoroquinolones and macrolides are the most effective antibiotics against *M. catarrhalis*, while fluoroquinolones and cefotaxime or ceftriaxone are the most effective antibiotics against *H. influenzae.* Since in most patients with sinusitis, otitis media, and CAP, there is no need to differentiate between species, and since multiple pathogens may be the cause of the same disease, it is rational to prescribe antibiotics which cover all causative microorganisms. Moreover, the difference in the form and cost of drugs plays an important role in the management of outpatients and inpatients. Considering all these points, fluoroquinolones and macrolides are recommended for the management of outpatients, and fluoroquinolones, macrolides, or ceftriaxone are recommend for the management of inpatients. In addition, in order to prevent or reduce any additional drug resistance to fluoroquinolones, second-line therapy is recommended, which includes macrolides and amoxicillin-clavulanate for the management of outpatients and macrolides, ceftriaxone, or amoxicillin-clavulanate for the management of inpatients. Prescription of β-lactams and/or co-trimoxazole would be ineffective.

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