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Review

Literature Review of Safety Event Reporting in Observational Studies: Challenges Extrapolating across Comparable Products

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Abstract: Nirmatrelvir/ritonavir (PAXLOVID^{TM}, Pfizer) is an anti-infective inhibiting CYP3A4 indicated for the treatment of COVID-19 in adults at increased risk of severe COVID-19. As a newly approved product, PAXLOVID has limited safety information regarding rare events and serious adverse events (SAEs). This review describes the characterization of the real-world safety profile of products with similar pharmacological properties to PAXLOVID and aims to understand the impact of any drug interaction on the concomitantly prescribed products. A literature search of articles in PubMed published between 2018 and 2023 was conducted to assess the real-world frequency of safety outcomes of interest, specifically those meeting the criteria of serious adverse reaction. The review was restricted to observational, noninterventional studies and included CYP3A4 inhibitors prescribed for short-term treatment of infections in the outpatient setting. Twenty-one articles were included in the review. Most focused on a small, predefined list of safety outcomes and did not provide insight into the broader range of safety outcomes that might occur for the evaluated products with similar pharmacological properties to PAXLOVID or the impact of any interaction on the concomitant product. The findings highlight the challenges in obtaining proxy safety outcomes characteristics via a review of products with comparable pharmacological properties and underscore the need to have large, rapidly accessible data sources that can contribute to the safety profile of newly authorized products in the real world.

Keywords: drug safety; nirmatrelvir/ritonavir; PAXLOVID; real-world data; serious adverse events

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1. Background and Rationale

Drug safety profiles, initially developed in clinical trials, continue to evolve as post-authorization data are accrued. Intrinsic elements of clinical trial design (e.g., strict eligibility criteria and limited duration) limit the potential to exhaustively detect rare safety events such as the incidence of serious adverse events (SAEs) or drug–drug interactions. Full characterization of the safety profile of a newly approved product is essential to provide patients and their prescribers comprehensive information on risk–benefit considerations and requires a period of real-world data (RWD) accumulation. The time required for RWD accrual would be impacted by factors such as the health of the indicated population (e.g., younger adults with lower underlying risk for AEs and lower likelihood of comorbidities and comedications) and the size of the patient population (e.g., substantial proportions for vaccinations programs versus smaller patient populations for rarer conditions).

One exploratory method for acquiring proxy information on the safety characteristics of interest during the early post-authorization period is a real-world literature review on products with similar pharmacological properties. This approach was applied to nirmatrelvir/ritonavir (PAXLOVID^{TM}, Pfizer), an anti-infective inhibiting CYP3A4 that is indicated for the treatment of COVID-19 in adults who are at increased risk of progressing to severe COVID-19. The opportunity for drug interactions and potentially related safety

outcomes is expected to be greater in a real-world setting than in a clinical trial setting. The purpose of this targeted review was to characterize the interaction profile and the occurrence of safety outcomes of interest among real-world users of products with similar pharmacological properties to PAXLOVID, i.e., short-term anti-infective medications that are CYP3A4 inhibitors that are prescribed in primary care settings regardless of the bacterial, fungal, or viral target. Safety outcomes of interest observed for products with similar pharmacological properties to PAXLOVID were evaluated in the post-marketing primary care setting as proxies for comparable safety outcomes among PAXLOVID users.

2. Results

The application of predetermined search terms and filters (Supplementary Table S1) yielded 754 abstracts for review; after the application of the additional inclusion and exclusion screening criteria, 21 articles were included in the present review (Figure 1 and Table 1).

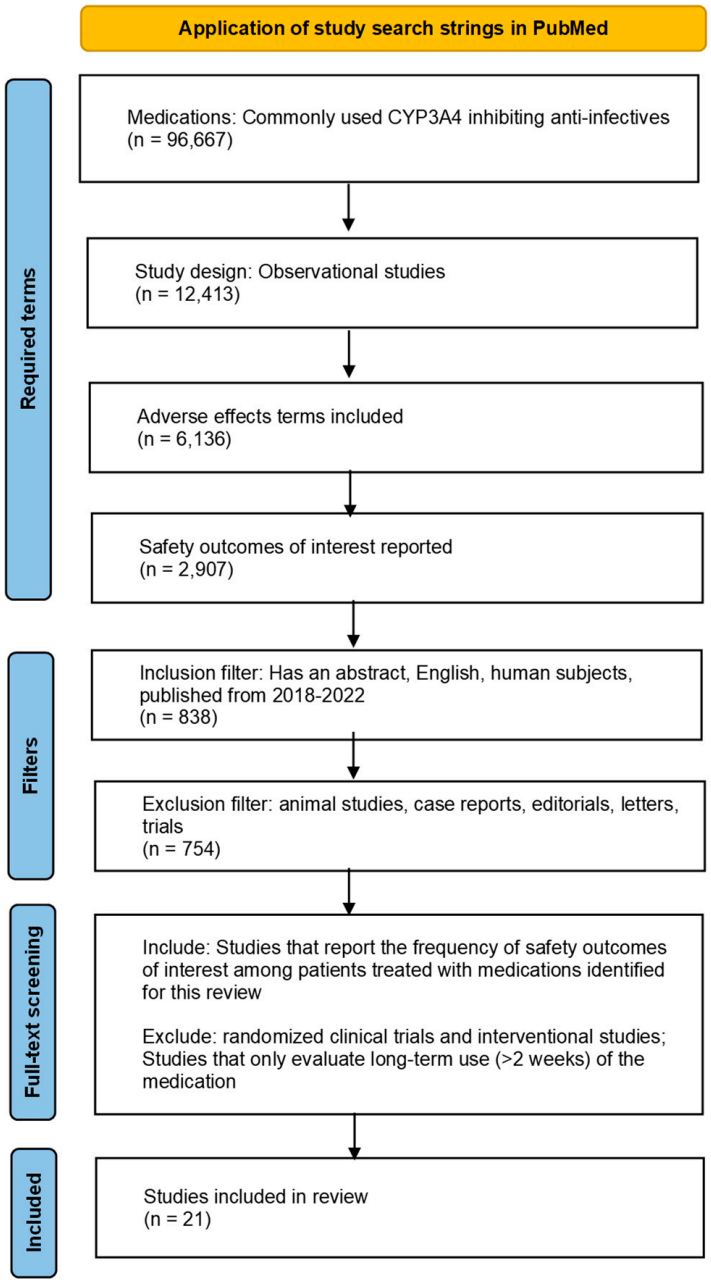

Figure 1. Targeted literature review search strategy and articles yielded.

Table 1. Characteristics of observational studies identified via a targeted literature review on selected products with similar pharmacological properties to PAXLOVID.

Author Year; Location; Study Years; Study Design.	**Population**	**Exposure (Drug)**	**Data Source**	**Safety Events and Outcomes of Interest**	**Frequency of Safety Outcomes of Interest: % Exposed Experiencing Event and/or Comparative Analysis If Provided**
Crellin 2018 [1]; UK; 1997–2015; Retrospective cohort	Patients aged 65+ y with UTI in UK CPRD and HES database	CIP, *n* = 15,594; AMX, *n* = 17,536	Rx for an antibiotic for a UTI after the latest of the following: 65th birthday; date of medical practice was data certified; or 1 y after practice registration date	Events with 14 d of therapy: 1. Acute kidney injury 2. Hyperkalemia 3. Death	Event frequency: CIP; AMX 1. Acute kidney injury 0.4%; 0.3% 2. Hyperkalemia 0.1%; 0.1% 3. Deaths 0.6%; 0.7% OR (95% CI), CIP vs. AMX: 1. Acute kidney injury 1.48 (1.03–2.13) 2. Hyperkalemia 1.17 (0.68–2.02) 3. Deaths 0.92 (0.73–1.15)
Inghammar 2018 [2]; Denmark; 1997–2011; Retrospective cohort	Patients aged 40–74 y in Denmark with infections eligible for study antibiotics	CLR, *n* = 187,887; Roxithromycin, *n* = 698,899; PEN controls, *n* = 3,473,081	Rx data from the Danish National Prescription Registry. Patients can contribute >1 course of therapy	CV death	Safety event within 0–7 d of initiation: CLR 5.0/1000 p-y, RR 1.66 vs. PEN Roxithromycin 1.9/1000 p-y, RR 0.88 vs. PEN
Jödicke 2018 [3]; Switzerland; 2014–2015; Retrospective cohort	Patients in Swiss claims database	CIP + tizanidine (coprescribed within a 7-d period), *n* = 199; Other antibiotic + tizanidine, *n* = 960	Rx claims data from large insurance company	Hospitalization event at 7, 14, and 30 d after co-Rx of interacting drugs	% experiencing safety event; OR (95% CI): 7 d: 4.0%; 2.19 (0.88–5.02) 14 d: 4.0%; 1.52 (0.63–3.33) 30 d: 6.5%; 1.68 (0.84–3.17)
Latif 2018 [4]; Pakistan; 2016–2017; Prospective cohort	Patients with *H. pylori* infection	CLR + AMX + omeprazole, *n* = 150; LVX + AMX + omeprazole, *n* = 150	Study drugs were provided to participants [1]	Signs or symptoms observed or reported at d 7 and 14 (no safety outcome type specified)	0% No safety outcomes reported in either group

Table 1. *Cont.*

Author Year; Location; Study Years; Study Design.	Population	Exposure (Drug)	Data Source	Safety Events and Outcomes of Interest	Frequency of Safety Outcomes of Interest: % Exposed Experiencing Event and/or Comparative Analysis If Provided
Mosholder 2018 [5]; UK; 2000–2013; Retrospective cohort	Patients aged 40–85 y, enrolled in a primary care database, no stroke or MI up to 90 d before Rx date	CLR, *n* = 287,748; DOX, *n* = 267,729; ERY, *n* = 442,999	Rx for study drug the UK CPRD from 2000 to 2013; patients needed to have a 1-y minimum washout for Rx of any study drugs	1. ACM 2. AMI 3. Stroke	1. ACM: CLR 7.9%, DOX 4.2%, ERY 7.3%; HR (95% CI): CLR vs. DOX 1.23 (1.20–1.25); CLR vs. ERY 1.13 (1.11–1.15); ERY vs. DOX 1.09 (1.06–1.11) 2. AMI (% not reported); HR (95% CI): CLR vs. DOX 1.13 (1.06–1.20); CLR vs. ERY 1.03 (0.98–1.07); ERY vs. DOX 1.10 (1.04–1.17) 3. Stroke (% not reported); HR (95% CI): CLR vs. DOX 1.15 (1.08–1.22); CLR vs. ERY 1.04 (1.00–1.09); ERY vs. DOX 1.10 (1.04–1.17)
Pasternak 2018 [6]; Sweden, 2006–2013; Retrospective cohort	Patients aged ≥ 50 y in Swedish registry	Oral FLQ, *n* = 360,088; AMX, *n* = 360,088	Outpatient Rx dispensing	Aortic aneurysm or dissection	FLQ: 0.02%; incidence 1.2/1000 p-y; AMX: 0.01%; incidence 0.7/1000 p-y
Pasternak 2018 [7]; Sweden and Norway; 2006–2015; Retrospective cohort	Pregnancies with singleton live births and stillbirths from national registry data	FLZ, *n* = 10,669; Non-FLZ, *n* = 106,690	FLZ Rx within 28 d before conception	Stillbirth or neonatal death	FLZ: 0.27% Non-FLZ: 0.35%
Berard 2019 [8]; Canada; 1998–2015; Case-control, nested	Pregnant women with outcome of SA (*n* = 320,868) or MCM (*n* = 226,599)	FLZ low dose ≤ 150 mg (SA cases *n* = 345, controls *n* = 1356; MCM cases *n* = 92, controls *n* = 821) FLZ high dose > 150 mg (SA cases *n* = 249, controls *n* = 642; MCM cases *n* = 50, controls *n* = 350)	Rx for oral FLZ filled from the Quebec Prescription Drug Insurance database, using dispensing date and duration of treatment For MCM, exposure was in the first trimester only	1. SA 2. MCM in the first 6 mo	1. SA: FLZ low dose: 1.2%, OR 2.23 (1.96–2.54) FLZ high dose: 0.9%, OR 3.20 (2.73–3.75) 2. MCM: FLZ low dose: 0.5%, OR 1.08 (0.87–1.34) FLZ high dose: 0.3%, OR 1.30 (0.97–1.75)

Table 1. *Cont.*

Author Year; Location; Study Years; Study Design.	Population	Exposure (Drug)	Data Source	Safety Events and Outcomes of Interest	Frequency of Safety Outcomes of Interest: % Exposed Experiencing Event and/or Comparative Analysis If Provided
Jeong 2019 [9]; Canada; 2008–2015; Retrospective cohort	Outpatient kidney transplant recipients (≥1 y after transplant)	Among patients, coRx calcineurin inhibitors: CLR or ERY, *n* = 112; AZM, *n* = 181	Pharmaceutical Information Network containing Rx data in Alberta, Canada	Within 30 d of coRx: 1. Composite of all-cause hospitalization, acute kidney injury, or ACM 2. All-cause hospitalization 3. Acute kidney injury (as ≥0.3 mg/dL serum creatinine increase or 1.5 times baseline)	1. Composite outcome: CLR/ERY 17%, AZM 10.5%; OR 1.74 (95% CI, 0.88–3.46) 2. Hospitalization: CLR/ERY 9.8%, AZM 3.3%; OR 3.18 (95% CI, 1.14–8.84) 3. Acute kidney injury: CLR/ERY 14.3%, AZM 9.4%; OR 1.61 (95% CI, 0.78–3.33)
Williamson 2019 [10]; UK; 1997–2016; Retrospective cohort	Patients with chronic rhinosinusitis, ≥1 Rx of MAC or PEN in CPRD, HES databases	MAC, *n* = 12,833; CLR, *n* = 5299; PEN, *n* = 53,498	Pharmacy dispensing data	1. ACM 2. Cardiac death 3. MI 4. Stroke 5. PVD 6. CA	1. ACM: MAC 4.7%; CLR 3.9%; PEN 5.0%. 2. Cardiac death: MAC 0.9%; CLR 0.6%; PEN 1.3% 3. MI: MAC 1.4%; CLR 1.0%; PEN 1.4% 4. Stroke: MAC 1.2%; CLR 0.9%; PEN 1.3% 5. PVD: MAC 1.0%; CLR 0.7%; PEN 1.0% 6. CA: MAC 2.2%; CLR 1.6%; PEN 2.1%
Baik 2020 [11]; USA; 2007–2016; Retrospective cohort	Medicare patients with inpatient and outpatient claims	CIP, *n* = 234,994; LVX, *n* = 155,991; MOXI, *n* = 14,728	Medicare Part D outpatient Rx drug records 2007–2016, exposure from dispensing date to the end of days of supply	Tendon rupture; 10-y rates post-Rx	CIP 3.7% LVX 3.8% MOXI 5.2% No antibiotic use 2.9%
Hill 2020 [12]; Canada; 2009–2016; Retrospective cohort	Outpatients taking an anticoagulant in linked databases for Ontario region	CLR, *n* = 6592; AZM, *n* =18,351	Outpatient Rx dispensing records for all adults >65 y, with an error rate of <1%	Major bleeding events leading to hospitalization within 30 d of antibiotic dispensing	CLR: 0.77% AZM: 0.43% Adjusted HR (95% CI): 1.71 (1.20–2.45)

Table 1. *Cont.*

Author Year; Location; Study Years; Study Design.	Population	Exposure (Drug)	Data Source	Safety Events and Outcomes of Interest	Frequency of Safety Outcomes of Interest: % Exposed Experiencing Event and/or Comparative Analysis If Provided
Mordi 2020 [13]; Scotland; 2004–2014; Retrospective cohort	Patients participating in the Genetics of Diabetes Audit and Research Tayside Scotland study	Total unique patients: CLR, *n* = 11,489 AMX, *n* = 36,537 Total prescriptions: CLR, *n* = 34,074 AMX, *n* = 171,153	Database of community prescribing data	1. CV hospitalization 2. Hospitalization for MI 3. CV mortality 4. ACM	At 0–14 d, 15–30 d, and 30 d–1 y, respectively: 1. CV Hospitalization: CLR, 1.6%, 1.3%, 5.4%; AMX, 1.4%, 1.2%, 6.6% 2. Hospitalization for MI: CLR, 0.1%, 0.07%, 0.5%; AMX, 0.1%, 0.08%, 0.6% 3. CV mortality: CLR, 0.2%, 0.2%, 1.5%; AMX, 0.3%, 2.3%, 1.0% 4. ACM: CLR, 0.8%, 0.8%, 4.5%; AMX, 1.0%, 1.0%, 5.8%
Fung 2021 [14]; USA; 2007–2016; Retrospective cohort	Medicare patients with inpatient and outpatient claims	CIP *n* = 343,320; LVX *n* = 239,083; MOXI *n* = 26,528; AZM *n* = 446,943; CLR *n* = 54,805; ERY *n* = 11,695; FLZ *n* = 116,539	Medicare Part D Rx claim with dispensing date, with short-term use cutoff at median 30 d supply	VA or SD	HR (95% CI) for VA/SD vs. nonusers: LVX: 1.51 (1.44–1.57) MOXI: 1.23 (1.03–1.45) ERY: 1.63 (1.32–2.02) FLZ: 2.23 (2.15–2.32)
Noergaard 2021 [15]; Denmark; 1997–2016; Retrospective cohort	All registered pregnancies in a nationwide register, 1 January 1997, to 31 December 2016	CIP: ≥1 Rx for systemic CIP within the first 22 wk (miscarriage) or first 12 wk (MCM) of pregnancy, *n* = 2050 Non-CIP: no Rx of any quinolones up to 3 mo before the LMP date to the pregnancy end date, *n* = 8200	Medical Birth Registry, the National Hospital Registry, the Danish National Prescription Registry and Statistics Denmark	1. Miscarriage 2. MCM	1. CIP: 8.3%, non-CIP: 8.7% 2. CIP: 3.4%, non-CIP, 3.4%

Table 1. *Cont.*

Author Year; Location; Study Years; Study Design.	Population	Exposure (Drug)	Data Source	Safety Events and Outcomes of Interest	Frequency of Safety Outcomes of Interest: % Exposed Experiencing Event and/or Comparative Analysis If Provided
Assimon 2022 [16]; USA; 2007–2017; Retrospective cohort	Patients with hemodialysis-dependent kidney failure	AZM, *n* = 188,871; LVX, *n* = 110,230	Outpatient study antibiotic Rx fills in the US Renal Data System. Treatment episodes = 180-d baseline, 30-d washout, and 10-d follow-up period	Sudden cardiac death: death due to CA or CA listed as the primary cause	Treatment d 1–5 AZM: 0.13%, 12.8/100K p-d LVX: 0.16%, 20.1/100K p-d Days 6–10 AZM: 0.11%, 10.4/100K p-d LVX: 0.13%, 17.8 100K p-d
Liao 2022 [17]; Taiwan; 1999–2013; Retrospective cohort (nested case–control)	Patients with T2D	Cephalosporins, *n* = 2212; PEN, *n* = 220; FLQ, *n* = 909; MAC, *n* = 131; Sulfonamide, *n* = 514; Tetracycline, *n* = 128; Metronidazole, *n* = 82	Taiwan NHIRD; Nationwide database includes all prescribed antibiotics	Up to 7 d after oral antibiotic use: Hypoglycemic emergency (hypoglycemia diagnosed in the emergency department)	Adjusted OR (95% CI): Cephalosporins 6.12 (5.74–6.52), PEN 3.10 (2.61–3.69), FLQ 12.05 (10.66–13.61), MAC 6.85 (5.91–7.96), Sulfonamide 7.20 (6.29–8.24), Tetracycline 2.13 (1.71–2.64), Metronidazole 3.64 (2.68–4.94)
Muanda 2022 [18]; Canada; 2008–2020; Retrospective cohort	Adults aged ≥66 y with advanced CKD	New Rx for a single oral FLQ (CIP, LVX, or norfloxacin) dispensed from an outpatient pharmacy; High-dose FLQ, *n* = 5482; Low-dose FLQ, *n* = 5516	Linked administrative healthcare databases in Ontario, Canada; excluded patients discharged from the hospital or emergency department within 2 d before the index date of Rx	Composite of a hospital visit with nervous system and/or psychiatric disorders, hypoglycemia, or collagen-associated events within 14 d of starting a new fluoroquinolone Rx	High dose: 1.2%; Low dose: 0.9%; High dose vs. low dose fluoroquinolone, weighted RR 1.45 (1.01–2.08)
Tan 2022 [19]; USA; 2002–2018; Retrospective cohort	Patients aged ≥ 18 y, receiving colchicine and either a macrolide or nonmacrolide antibiotic	cMAC, *n* = 2199; Non-cMAC, *n* = 12,670	CERNER Health Facts EMR database	1. Rhabdomyolysis 2. Pancytopenia 3. Muscular weakness 4. Heart failure 5. Acute hepatic failure 6. ACM	1. Rhabdomyolysis: cMAC 0.8%; Non-cMAC 0.7% 2. Pancytopenia: cMAC 4.7%; Non-cMAC 5% 3. Muscle weakness: cMAC 0.3%; Non-cMAC 0.3% 4. Heart failure: cMAC 18.3%; Non-cMAC 9.1% 5. Acute hepatic failure: cMAC 0.9%; Non-cMAC 0.7% 6. ACM: cMAC 3.9%; Non-cMAC 2.3%

Table 1. *Cont.*

Author Year; Location; Study Years; Study Design.	Population	Exposure (Drug)	Data Source	Safety Events and Outcomes of Interest	Frequency of Safety Outcomes of Interest: % Exposed Experiencing Event and/or Comparative Analysis If Provided
Wang 2022 [20] USA; 2003–2015; Retrospective cohort	Adults aged ≥18 y, initiated an oral FLQ or comparator antibiotic, and diagnosed with pneumonia or UTI 3 d before drug initiation	Pneumonia cohort (matched): FLQ (CIP, LVX, MOXI, other), *n* = 275,521; AZM comparator, *n* = 275,521 UTI cohort (matched): FLQ (CIP, LVX, MOXI, other), *n* = 1,102,613; TMP-SMX comparator, *n* = 1,102,613	Pharmacy dispensing data; claims and encounters from US health insurance claims database (IBM Marketscan)	Hospital admission or emergency department visit for suicidal ideation or self-harm within 60 d after treatment initiation	Pneumonia cohort: FLQ: 0.03%; AZM: 0.03% HR (95% CI) 1.01 (0.76–1.36) UTI cohort: FLQ 0.04%; TMP-SMX 0.04% HR (95% CI) 1.03 (0.91–1.17)
Yu 2022 [21]; Taiwan; 2000–2016; Retrospective cohort	Patients diagnosed with coronary heart disease	CLR, *n* = 9631; non-CLR, *n* = 9631	Taiwan Longitudinal Generation Tracking Database; new prescription for CLR propensity matched by date with nonusers	1. ACM; 2. CV mortality; 3. Non-CV mortality	1. ACM: CLR 8.9%; non-CLR 7.0% 2. CV mortality: CLR 2.0%; non-CLR 1.7% 3. Non-CV mortality: CLR 6.9%; Non-CLR 5.3%

ACM = all-cause mortality; AMI = acute myocardial infarction; AMX = amoxycillin; AZM = azithromycin; CA = cardiac arrhythmia; CI = confidence interval; CIP = ciprofloxacin; CKD = chronic kidney disease; CLR = clarithromycin; cMAC = colchicine plus macrolide antibiotic; CPRD = Clinical Practice Research Datalink; CV = cardiovascular; d = day; DOX = doxycycline; EMR = electronic medical record; ERY = erythromycin; FLQ = fluoroquinolones; FLZ = fluconazole; HES = Hospital Episodes Statistics; HR = hazard ratio; LMP = last menstrual period; LVX = levofloxacin; MAC = macrolide; MCM = major congenital malformations; MI = myocardial infarction; mo = month; MOXI = moxifloxacin; NHIRD = National Health Insurance Research Database; OR = odds ratio; p-d = person days; PEN = penicillin; PVD = peripheral vascular disease; p-y = person years; RR = relative risk; Rx = prescription; SA = spontaneous abortion; SAE = severe adverse event; SD = sudden death; T2D, type 2 diabetes; TMP-SMX = trimethoprim-sulfamethoxazole; UK = United Kingdom; USA = United States of America; UTI = urinary tract infection; VA = ventricular arrhythmias; wk, week; y = year.

Most studies included in this review were retrospective cohort studies, with more than half of the patient populations characterized by a particular medical condition or infection type (Table 1). Specifically, study populations included patients with chronic rhinosinusitis [10], type 2 diabetes [17], kidney transplant recipients [9], hemodialysis-dependent kidney failure [16], or coronary heart disease [21], older adults with advanced chronic kidney disease [18], pregnant women [7,8,15], patients with *Helicobacter pylori* infection [4], urinary tract infection [1,20], or pneumonia [20]. The remaining studies included patient populations drawn from the general population [2,3,5,6,11–14,19].

The majority of studies had either a single predefined safety outcome of interest or a limited number of predefined safety outcomes of interest; only two of the studies included in this review had a broader definition for safety outcome reporting (i.e., any safety outcome [4], or any hospitalization event [3]) (Table 1). Of the seven studies with a single safety outcome of interest, the outcomes included tendon rupture [11], major bleeding events [12], sudden cardiac death [16], hypoglycemic emergency [17], cardiovascular death [2], suicidality [20], or a composite outcome of nervous system or psychiatric disorders, hypoglycemia, or collagen-associated events [18]. The remaining 13 studies included 2–6 endpoints per paper [1,5–10,13–15,19].

Drug interactions leading to safety outcomes of interest were a focus of research in three papers [3,9,12]. Each was designed with specific pairs of known CYP3A4 inhibitor and substrate drugs or drug classes. None of these studies conducted broad screening and quantification of safety outcomes arising from potential drug interactions.

3. Discussion

The results of this review indicate that the method of selection of products with similar pharmacological properties to PAXLOVID does not contribute materially to characterizing the safety profile of a new drug such as PAXLOVID. Studies examining safety outcomes secondary to drug interactions were few and were specific to interacting combinations or outcomes.

3.1. Outcome Generalizability

Rather than evaluating the frequency of all safety outcomes, several studies were designed to evaluate the selected drug with a specific safety outcome (e.g., clarithromycin association with cardiac events). Other studies selected co-administered drug pairs to evaluate a specific drug interaction event. In the few studies without predefined safety outcomes of interest, either no data were available on the diagnosis related to the hospitalization outcome [3] or no safety outcomes occurred during the study period [4]. Accordingly, the results of this literature review cannot be considered representative of all safety outcomes that occur for the short-term CYP3A4 inhibitor anti-infective medications under review.

3.2. Patient Representativeness

The demographic and disease characteristics of patients identified in observational studies may not be generalizable to the entire population using the reference drug. For example, some studies gathered specific cohorts of dialysis patients, pregnant patients, patients with diabetes, or elderly patients. While results from special patient cohorts have limited generalizability to a broader patient population, results on products with similar pharmacological properties may still be of interest because they may address the evidence gaps often present in special patient populations; however, the potential for filling evidence gaps depends on the outcomes selected (per point 5.1 above). Similarly, results from patient populations that were selected due to specific infections may have limited potential for generalizability to potential users of PAXLOVID who were infected with COVID-19. The challenge of patient generalizability with respect to the relevant infection could not be avoided in the absence of products that are more directly comparable with PAXLOVID (i.e., an oral treatment indicated for COVID-19).

3.3. Setting

Outpatient settings can be highly variable with respect to the burden of illness and patient type. Exposures and behaviors that affect outcomes may not be well documented in this setting.

3.4. Exposure Definition

Selection of an appropriate exposure product with similar pharmacological properties to PAXLOVID is challenging. Although the selected anti-infectives are CYP3A4 inhibitors, the level of inhibition may differ, which may affect the outcome, particularly when addressing drug–drug interactions. Differences in chemical structure and product indication would additionally impact the extent to which safety outcomes for products selected for this review could be extrapolated to PAXLOVID. Additionally, other pharmacokinetic and pharmacologic characteristics of the antibiotic and antifungal agents, such as product half-life and mechanism of action, may limit suitability for comparison to the reference antiviral. Lastly, since CYP3A4 inhibition leads to increased exposure to concomitantly prescribed medicines, characterization of the interaction profile associated with CYP3A4 inhibitors would also require collecting a complete list of concomitant medications with well-defined safety profiles.

4. Methods

This literature search was conducted in PubMed on 16 December 2022 and was restricted to English-language articles published between 2018 and 2023; full details of the search strings are presented in Supplementary Table S1. There were no geographic limits. The review included the following CYP3A4 inhibitors prescribed for patients >11 years old for the short-term ($\leq$14 days) treatment of infections in the outpatient setting: clarithromycin, erythromycin, itraconazole, fluconazole, ketoconazole, posaconazole, ciprofloxacin, levofloxacin, and ofloxacin. To support the objectives of this review, products with CY3A4 inhibition were selected. The focus was on the interaction profile that could lead to the real-world reporting of safety outcomes of interest. This review was restricted to observational, noninterventional studies to assess the real-world frequency of the safety outcomes of interest reported. For this review, safety outcomes of interest were those that met the criteria of "serious", as defined by study authors, or if hospitalization or death was specified in the outcome definition.

5. Conclusions

In this review, most of the studies focused on a small, predefined list of safety outcomes of interest; therefore, they do not provide insight into the broader range of safety outcomes that might occur for the treatments included in this review. This limited scope, coupled with highly selected patient populations, renders it difficult to extrapolate a general profile of safety outcomes among users of products with similar pharmacological properties to PAXLOVID.

There may be greater potential to gain insight into a new product safety profile via a literature review approach for a product where a more directly comparable treatment can be selected, that is, limiting the search to drugs in the same class, with similar metabolism, indicated for the same condition and similar patient population. However, even under such circumstances, there may be limited potential to further understand the contribution of drug–drug interactions to the observed safety outcomes; in the present review, studies either did not comment on such attribution or were designed specifically to examine safety outcomes in the context of coadministered drug pairs. Because information is not readily available in the literature, an iterative process of search and analysis may be needed to characterize and estimate the rate of potential safety outcomes associated with drug–drug interactions for a new agent such as PAXLOVID. Overall, the results of the present literature review indicate that observational research typically analyzes a prespecified short list of safety outcomes in targeted special patient populations. This suggests that, even for a

more limited patient population/more directly comparable product, limitations in the characterization of safety outcomes will occur.

In conclusion, the exploratory method did not yield the proxy information that was of interest. This targeted literature review highlights the challenges in obtaining proxy safety outcome characteristics via comparison with products with similar pharmacological properties to those in the observational setting and underscores the need to have large, rapidly accessible data sources that can contribute to the safety profile of newly authorized products in the real world.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/pharma2040029/s1. Table S1. Search strings, executed on 11 January 2023.

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Conflicts of Interest: Heather Ward is an employee of Pfizer. Robert Massouh is a former employee of Pfizer. Bao-Anh Nguyen-Khoa reports no potential conflict of interest at this time.

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