The Open Public Health Journal
DOI: 10.2174/0118749445441515260415101759, 2026, 19, e18749445441515
ISSN: 1874-9445
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MINI-REVIEW **OPEN ACCESS**

The Evolution of the Use of Oseltamivir (Tamiflu®) in Seasonal and Pandemic Influenza: A Review of Recommendations from Market Approval to Present Day

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Abstract:

Oseltamivir phosphate, also known as Tamiflu®, is a neuraminidase inhibitor antiviral drug that has been a key intervention for the treatment and prevention of influenza since its market approval in 1999. Despite widespread acknowledgement of oseltamivir as a first-line treatment for severe influenza, its prescribing and use have been subject to debate over the years, as evidence has continually emerged challenging the magnitude of its benefits. Recommendations and advice published by the World Health Organization (WHO) have been updated several times since the organisation first endorsed the drug in 2002, in response to the current global situation and the best available evidence at the time. Oseltamivir gained particular prominence during the H1N1 swine flu pandemic in 2009, with various countries utilising stockpiles and ethical reviews of its distribution. The aftermath of this event prompted huge research activity, including multiple Randomized Controlled Trials (RCTs) and seminal Cochrane Reviews, which led to an evolution in recommendations by guideline developers. In light of recent changes to the WHO treatment guidelines, this comprehensive narrative review aims to examine key events in the history of oseltamivir, marked by changes in guideline recommendations and the publication of seminal papers in the field. To our knowledge, this review paper is the first to present a chronological analysis of research on oseltamivir alongside key events in guideline development, offering a key insight into the background and context of this antiviral therapeutic and prophylactic drug.

Keywords: Oseltamivir phosphate, Tamiflu, Influenza, Antiviral drug, Neuraminidase inhibitor, Seasonal pandemic, Prophylaxis.

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Cite as: Williams M, Parlour R, Quintyne K, O'Moore É. The Evolution of the Use of Oseltamivir (Tamiflu®) in Seasonal and Pandemic Influenza: A Review of Recommendations from Market Approval to Present Day. Open Public Health J, 2026; 19: e18749445441515. http://dx.doi.org/10.2174/0118749445441515260415101759

Received: September 19, 2025
Revised: November 17, 2025
Accepted: December 24, 2025
Published: June 24, 2026

1. INTRODUCTION

The antiviral drug oseltamivir phosphate, known commercially as Tamiflu®, has received considerable attention both in the clinical research community and from the general public since its development in the 1990s [1]. Oseltamivir belongs to the Neuraminidase Inhibitor (NAI) class of drugs, and its role in treating and preventing influenza disease has prompted numerous discussions on political and ethical challenges related to pandemic preparedness [2-4]. Oseltamivir's history has been marked by several key events: its market approval in 1999, the H1N1 pandemic in 2009, and the present-day growing threat of avian influenza. In terms of antiviral mode of action, oseltamivir inhibits the enzyme neuraminidase present on the surface of the influenza virus. It is a competitive inhibitor, acting as a sialic acid agonist to compete with the neuraminidase binding site, preventing virus escape and entry into neighbouring host cells [5]. Prior to the Food and Drug Administration (FDA) approval of oseltamivir as an influenza therapy in 1999, M2 inhibitors were the primary class of drugs available on the market [6]. However, these did not act against influenza B. The development of oseltamivir, and indeed of NAIs, heralded a new era in influenza treatment, offering a broader spectrum of activity and a lower potential for resistance [7].

Globally, influenza presents a significant threat to the health and well-being of at-risk populations. The World Health Organization (WHO) estimates that seasonal influenza may result in approximately 290,000 – 650,000 deaths annually at a global level, and it is estimated that annual influenza epidemics result in 3-5 million cases of severe illness a year [8]. In Ireland during the 2024/2025 flu season, between weeks 40 2024 to week 20 2025, there were 243 Intensive Care Unit (ICU) admissions and 330 deaths notified [9].

Considering recent key changes to oseltamivir recommendations published in WHO guidelines [10], this paper aims to examine the history of oseltamivir through a critical lens and to identify key milestones in research leading to its current role in treating and preventing severe influenza disease. While specific aspects of the background evidence for oseltamivir and the lessons learned have previously been examined in published papers [2], a parallel, chronological commentary on guideline recommendations published during this time is, to our knowledge, presented for the first time in this paper.

2. METHODS

Narrative review methods were used to synthesise and interpret the existing literature on the topic of oseltamivir as an antiviral drug. Three electronic databases (MEDLINE Ovid, Embase, and PubMed) were searched using defined Boolean operators developed from key concepts related to the topic. Studies meeting the inclusion criteria (RCTs, relevant case studies, clinical trial reporting, and systematic reviews) were considered for this review. Date limits were applied to exclude papers published before 1999, and only papers available in the English language were included. Two-stage screening was carried out to assess relevancy of studies, and a sample of the included studies was validated by another independent reviewer to reduce bias. A grey literature search of key sources (including the WHO, FDA, and CDC websites) was also conducted to supplement the above methods and provide background and context for the chronological review. A summary of key milestones and time periods was also constructed, and is available in Table **1**.

2.1. Review of Key Milestones and Time Periods

2.1.1. 1999-2008 – Market Approval and Initial Studies

Oseltamivir, the first neuraminidase inhibitor, was developed by Hoffmann-La Roche and tested *via* rigorous three-phase clinical trials before market approval in 1999 [11]. The WHO endorsed oseltamivir as a therapeutic strategy in 2002 and drafted preliminary recommendations around its usage in 2004 [12]. Oseltamivir was initially widely recommended across the USA, Europe, and Asia for the treatment of seasonal and pandemic influenza, particularly in high-risk groups (*e.g.*, the elderly, immunocompromised individuals, or those with chronic illnesses). In 2004, Japan became the largest consumer of oseltamivir, recommending the drug for treatment and prophylaxis of influenza [2, 13].

Amid concerns about H5N1 (avian influenza) in 2006-2007, many countries, including France, purchased large stockpiles of oseltamivir. In the USA, a stockpile of oseltamivir sufficient to treat 25% of the population was maintained under the Pandemic and All-Hazards Preparedness Act (PAHPA) 2006 [14, 15].

While many countries' stockpiles grew, the WHO raised concerns in 2006 about the growing threat of oseltamivir resistance. These concerns arose from increased prescribing and from findings that the drug was not degraded during standard sewage treatment [16]. Indeed, an Influenza virus (H1N1) resistant to oseltamivir was first detected in Norway in January 2008 and subsequently spread throughout much of the Northern Hemisphere [17, 18].

The threat of an influenza pandemic at the time prompted discussions about the ethics of distributing antivirals, including oseltamivir. In response, the WHO conducted a global consultation on ethical planning for influenza pandemics [19]. Subject matter experts suggested a 'fair innings' approach to distribution of antiviral drugs and argued the importance of ensuring access to antivirals in lower-income countries [4]. A framework was developed in 2008 for addressing these ethical concerns. This framework outlined prioritisation for treating healthcare workers and people at higher risk of severe influenza disease during pandemics [20].

Table 1. Information on milestones sourced *via* World Health Organization (WHO), Food and Drug Administration (FDA), U.S. Centers for Disease Control (CDC) and European Medicines Agency (EMA) websites. Accessed on 17 November 2025.

Year	International	USA (FDA, CDC)	Europe (EMA/EMEA)
1999 – First approval	-	The FDA recommends the use of oseltamivir for the treatment of influenza in adults [11].	-
2000	-	Oseltamivir approved for children >1 year old. Approved for prophylaxis in adults [38]	-
2002	-	-	Oseltamivir is approved across the EU for treatment and prophylaxis of influenza [81].
2008	-	FDA updates oseltamivir label to include warning regarding the possibility of neuropsychiatric side effects in children and adolescents [38, 54].	EMA notes psychiatric events in the product information leaflet [81]
2009 – H1N1 Pandemic	WHO emphasises early treatment for those with severe illness and those in higher-risk groups [10].	The FDA recommends the use of oseltamivir for the treatment of confirmed or suspected H1N1 [38].	EMA issues specific guidance for oseltamivir in the H1N1 pandemic. Recommendations for oseltamivir extended to infants <1 year of age for pandemic use [81].
2010	WHO publishes guidelines for Pharmacological Management of pandemic H1N1 influenza virus. Strong recommendation to treat patients with severe progressive illness early [30].	-	-
2011	Oseltamivir is listed as a core drug on the WHO Essential Medicines List [36].	-	-
2012	WHO guidance recommends treatment of severe or progressive influenza illness in all age groups (including neonates) [30].	FDA extends approval to infants older than 2 weeks of age [38].	-
2017	WHO treatment guidelines have been updated to reduce emphasis on the routine use of oseltamivir. Oseltamivir becomes a 'complementary' drug on the WHO Essential Medicines List [58].	-	-
2024	WHO updated its influenza treatment guidelines. Oseltamivir is no longer recommended for mild cases of influenza [10].	The CDC recommends oseltamivir as a first-line treatment for anyone suspected of acquiring Highly Pathogenic Avian Influenza (HPAI) [79]	-

Much of the clinical research published on Oseltamivir during this period focused on the drug's efficacy and safety [21-25]. Trials on the timing of administration and dosing strategies were also conducted [26, 27], and later, on combination therapies with other antivirals such as Zanamivir [28, 29]. Early studies found oseltamivir to be well-tolerated and provided evidence of reduced illness duration and severity, and a reduced likelihood of disease complications, particularly when administered within 48 hours of symptom onset [21-25]. It is worth noting that all but one of the identified Randomized Controlled Trials (RCTs) conducted during this period received financial support from Roche, the manufacturer of oseltamivir. In addition to concerns around bias and conflict of interest, it remained that oseltamivir had not yet been tested in a real-world pandemic scenario.

2.1.2. 2009-2011 – H1N1 Swine Flu Pandemic

The period from 2009-2011 represented a significant test of the efficacy and safety of oseltamivir, which had previously only been prescribed for seasonal influenza A and B. The April 2009 declaration of H1N1 swine flu as a Public Health Emergency of International Concern (PHEIC) ushered in a new era of learning about the use of influenza antivirals, including oseltamivir, and highlighted gaps in knowledge and significant shortfalls in drug availability and health inequities globally.

During the 2009 H1N1 pandemic, the WHO recommended widespread use of oseltamivir as first-line treatment for suspected and confirmed cases, particularly for those with severe disease, and people admitted to hospital [18, 30]. WHO guidelines on pharmacological

interventions for H1N1, published in 2010, specifically noted that patients with severe or progressive clinical illness should be treated with oseltamivir as soon as possible [30]. Many jurisdictions, including Australia and the UK, used their stockpile of oseltamivir during the H1N1 pandemic [31]. As per frameworks previously developed around its use in such scenarios, oseltamivir prescribing was prioritised for populations at high risk of developing severe disease, for example, pregnancy, extremes of age, and people with underlying health conditions [20]. Some clinical studies on oseltamivir were terminated early during this period; for example, a 2010 study comparing oseltamivir monotherapy to combination therapy with zanamivir by Duval *et al.*, so that results could be analysed early to inform prescribing during the pandemic [32]. This study concluded that during the pre-pandemic winter of 2009, when H3N2 viruses predominated (more than 85%) in France, the oseltamivir-zanamivir combination was less effective than oseltamivir monotherapy and not significantly more effective than zanamivir monotherapy in adults with seasonal influenza A virus infection [32]. Additionally, two studies were published examining the impact of early oseltamivir treatment in patients with influenza A: One was conducted prior to the declaration of a pandemic and focused on children [33], and the other was prompted by a desire to treat critically ill patients with urgency [34]. Both studies identified significant benefits in commencing oseltamivir treatment within 24 hours.

When the H1N1 pandemic was declared over by the WHO in August 2010 [35], oseltamivir continued to be routinely prescribed for seasonal influenza in patients at higher risk of developing severe disease. Oseltamivir was also recommended for the treatment of patients with confirmed or suspected pandemic influenza (H1N1) 2009 and severe or progressive illness, or those with confirmed or suspected pandemic influenza disease in particular risk groups, most notably pregnant women and infants. In 2011, owing in part to its role in the H1N1 pandemic, oseltamivir was listed as a 'core' drug on the WHO Essential Medicines List (EML) and was to be used in accordance with the WHO treatment guidelines [36].

The pandemic and its aftermath prompted numerous discussions about the purported benefits of oseltamivir, as well as the cost-effectiveness of the drug. In 2011, in a framework developed in the wake of the H1N1 pandemic, the WHO recommended introducing tiered pricing in developing countries to increase the affordability of vaccines and neuraminidase inhibitors, urging manufacturers to consider a country's income level when setting prices [37]. Publications began to emerge questioning the risk-benefit ratio of oseltamivir, particularly considering emerging adverse events associated with use of the drug. In three relevant randomised controlled trials published during this period, vomiting was listed in each one as the most common adverse event. However, despite these side effects, the majority of studies maintained that oseltamivir was a well-tolerated drug [32-34].

2.1.3. 2012-2016 – Evidence Base Grows

From 2012-2016, recommendations around oseltamivir underwent significant changes. These changes occurred as a result of increased research activity and were influenced by learning from the H1N1 pandemic.

In 2012, the United States Food and Drug Administration (FDA) approved oseltamivir for use in infants 2 weeks of age or older, with a maximum treatment duration of 2 days [38]. In Europe, the drug could only be prescribed to patients one year or older. The WHO also continued to monitor oseltamivir resistance, identifying only a small number of oseltamivir-resistant cases in 2012 [39]. Notably, in 2014 and 2016, the first generic forms of oseltamivir received market approval in Europe and the US, respectively [40, 41].

In research, the aftermath of the H1N1 pandemic led to a significant increase in publications on oseltamivir. As part of this review, we identified 12 relevant RCTs published between 2012 and 2016, all of which examined oseltamivir through various lenses, including optimal dosing strategies across multiple age groups, timing of administration, and comparisons with newer NAIs [34, 42-52]. These studies largely confirmed previous observations regarding the drug, favouring early administration and showing similar efficacy compared with zanamivir, lanamivir, and peramivir [44, 45, 47]. Different formulations of the drug were studied, including increasing the dosage to up to 150mg twice daily, extending the duration of treatment, and changing the method of administration. Three studies on higher-dose oseltamivir found no clinical benefit from increasing the dosage or duration of treatment, with no significant reduction in hospitalisation duration or time to symptom alleviation [43, 46, 48]. Another study on intravenous administration of oseltamivir in patients hospitalised with severe influenza was terminated early, with many of the trial participants switching to the oral form of the drug due to adverse effects [51]. A 2013 Thai RCT focusing on the safety and tolerability of oseltamivir and inhaled Zanamivir in healthy health and care workers observed that 17.8% (n=23) of those receiving oseltamivir had notable side effects, mostly gastrointestinal in nature [44].

Some studies published during this time questioned the magnitude of oseltamivir's benefits, particularly in individuals with non-severe influenza. Adverse events continued to be reported in studies of oseltamivir. Although these were largely gastrointestinal in nature, observations of neuropsychiatric events began to be reported. One study by Morimoto *et al* outlined the case of a 15-year-old girl suffering from delirium, insomnia, and visual hallucinations after being administered oseltamivir for influenza disease [53]. These symptoms disappeared following cessation of the drug. Later studies would confirm that the incidence of such events is significantly increased following oseltamivir administration [54]. A 2016 study of young children with influenza in Central America did not identify any significant reduction in duration of hospital stay [52].

As the evidence base expanded and real-world applications were tested, it became increasingly unclear whether the drug was cost-effective as a tool against seasonal influenza. Most notably, in 2012, a seminal Cochrane Review questioned the effectiveness of oseltamivir, suggesting it shortened symptoms by roughly 17 hours and had a limited impact on reducing hospitalisations and complications [55]. Following its publication, the authors of this study (the Acute Respiratory Infections Cochrane Review group) submitted a request to delete oseltamivir from the WHO EML. Despite this, oseltamivir remained on the EML in the 2013 report [56]. It was recommended that oseltamivir remain an essential medicine for potentially severe or complicated illness due to confirmed or suspected influenza, in accordance with WHO treatment guidelines [56]. Following growing pressure from the medical and public health community, the WHO and other organisations began to reduce emphasis on the routine use of the drug.

2.1.4. 2017-2020

WHO treatment guidelines were again changed in 2017 due to accumulating evidence that the effectiveness of the drug on relevant clinical outcomes in non-severe influenza disease may have been overestimated (*e.g.*, reductions in symptom duration and hospitalisation rates). In 2017, the WHO recommended restricting the use of oseltamivir to severe illness due to confirmed or suspected influenza virus infection in critically ill hospitalised patients, again placing less emphasis on routine use of the drug and acknowledging that its benefits are modest for otherwise healthy individuals. Furthermore, the focus shifted away from widespread prophylactic use due to concerns about drug resistance and cost-effectiveness [57].

As oseltamivir was the only antiviral listed on the EML that was licensed for use in patients with severe seasonal or pandemic influenza disease, the drug remained on the list despite being considered for deletion. However, it was moved from the ‘core’ list to the ‘complementary’ list in 2017 [58]. The 2019 EML report noted that the WHO were updating their treatment guidelines for oseltamivir, and that outright deletion from the list would be reconsidered following a review of more recent evidence [59].

During this time period, a number of RCTs were conducted that compared oseltamivir with new and alternative antiviral options and combination therapies, with mixed results overall. Two studies during this time compared oseltamivir with intravenous peramivir, demonstrating similar efficacy in reducing symptom duration and severity of clinical outcomes [60, 61]. The study by Nakamura *et al*., however, acknowledged that these results were modest and did not demonstrate superiority compared with oseltamivir [61]. One 2017 study on triple therapy with clarithromycin–naproxen–oseltamivir in patients hospitalised with influenza A (H3N2) demonstrated a significant reduction in mortality compared with oseltamivir alone [62]. Likewise, combination therapy with favipiravir and oseltamivir appeared to offer a clinical advantage over oseltamivir alone in a 2020 study of patients hospitalised with severe influenza, potentially accelerating time to symptom alleviation [63]. Conversely, another 2017 RCT on oseltamivir, amantadine, and ribavirin triple therapy did not demonstrate any significant clinical benefit compared with oseltamivir alone [64]. These results largely supported the assertion that oseltamivir may have some clinical benefit when administered to patients with critical illness due to influenza; however, the magnitude of effect may not fully extend to patients with mild-to-moderate symptoms.

Although oseltamivir resistance in seasonal influenza strains remained low, these concerns persisted and prompted the WHO to encourage the development of novel antiviral drugs. A promising new antiviral drug, baloxavir marboxil, was approved for use in Japan and the US in 2018. Baloxavir had a novel mode of action compared with oseltamivir and other neuraminidase inhibitors and gained prominence amid the growing threat of resistance to the latter group. A 2020 study comparing baloxavir to oseltamivir in children demonstrated that baloxavir reduced the time to alleviation of symptoms to (on average) 138.1 hours, compared with 150 hours of symptom duration in children who were administered oseltamivir [65]. This was consistent with a 2023 RCT on baloxavir in children (1-12 years of age), suggesting that this antiviral may be expanded for use in paediatric populations in the near future [66].

2.1.5. 2021-Present

Although a 12mg/ml formulation of oseltamivir was removed from the WHO EML in 2021, the 30mg, 45mg, and 75mg formulations of oseltamivir remain on the ‘complementary’ list for both adults and children [67]. However, it should be noted that the WHO has not undertaken a review of the drug's clinical efficacy since 2017 and has not signalled an intention to revise this in the near future. Patents on Tamiflu® have expired in most jurisdictions, and lower-cost generic forms continue to be made available [68].

During this time, research continued to yield mixed results [69-71]. Most notably, a large systematic review and meta-analysis was published by Hanula *et al*, which analysed 15 RCTs encompassing 6166 participants. This meta-analysis agreed with the earlier Jefferson *et al*. study and concluded that oseltamivir was not associated with a significant reduction in hospitalisations due to influenza [55, 72].

As of 2024, oseltamivir is no longer recommended for mild cases [10]. It is still advised for severe cases, hospitalised patients, and high-risk individuals. The WHO recommendations are reflected in Irish national guidelines; for example, the Guidance on the use of antiviral agents for the treatment and prophylaxis of Influenza recommends oseltamivir treatment for cases of severe influenza disease or non-severe disease in individuals at higher risk of severe outcomes [73].

The WHO now recommends that research focus shift toward improved diagnostics and vaccine strategies [74],

and that more emphasis be placed on rapid testing before prescribing antivirals [75]. The evidence base published during this time generally followed this trend. For example, a 2023 RCT on rapid diagnostic tests for influenza in long term care facilities showed an increase in the use of oseltamivir in these high-risk groups as a prophylactic strategy, significantly reducing the number of hospital admissions, length of stay, and visits to emergency departments [75]. However, a 2022 study on the quality-adjusted life years (QALY) gained by adding oseltamivir to usual care for influenza-like illness demonstrated modest results, suggesting that the QALY gain would be limited [70, 73]. While the WHO does not provide specific recommendations for Residential Care Facilities (RCFs) or other congregate settings, these are typically set at a national or European level. For example, Irish guidelines specifically recommend that residential care facilities have procedures in place to ensure timely access to oseltamivir in the event of an influenza outbreak [73]. Interim Guidelines published by the US Centers for Disease Control and Prevention (CDC) in 2024 contain clear RCF-specific recommendations for treatment and prophylaxis during outbreaks [76].

The growing threat of avian influenza and its potential to infect humans has prompted renewed concerns about neuraminidase inhibitors. Initial studies have suggested that H5N1 strains (in particular, clade 2.3.4.4b) circulating on poultry farms in Canada have shown resistance to oseltamivir [77]. This is purported to occur *via* the known oseltamivir resistance gene NA-H275Y. Interestingly, prior studies in humans have reported that resistance to oseltamivir *via* this mechanism does not confer cross-resistance to zanamivir, another neuraminidase inhibitor [78]. Despite this, oseltamivir is recommended by the CDC as a first-line treatment for anyone in the United States suspected of acquiring Highly Pathogenic Avian Influenza (HPAI) [79]. Additionally, in Ireland, a 10-day course of oseltamivir 75mg daily is recommended for post-exposure prophylaxis if a high-risk exposure with an HPAI-infected bird or mammal has occurred [80].

CONCLUSION

It is evident from this review of WHO recommendations, and how these evolved over the years, that the treatment guidelines were significantly influenced by the evidence base as well as real-world events and key policy decisions made during this time. Although we did not conduct a full systematic or rapid review, we reviewed the clinical outcomes from thirty-eight RCTs. Relevant outcomes were noted in this review. There was evidence in the studies reviewed to suggest that administration of oseltamivir may result in fewer deaths in higher-risk influenza patients; however, the majority of the RCTs we reviewed demonstrated a modest benefit or insufficient evidence, particularly for non-severe influenza. Many of the RCTs included in this review declared conflicts of interest in the form of industry funding, which could be considered a limitation. In summation, while oseltamivir remains a clinically relevant drug for higher-risk influenza cases, it is likely that recommendations will continue to evolve as more RCTs on oseltamivir are conducted over the coming years, possibly reducing emphasis on routine use of the drug and paving the way for treatment regimens that also include newer antivirals.

AUTHORS' CONTRIBUTIONS

The authors confirm their contributions to the paper as follows: M.W.: Contributed to manuscript preparation; M.W. and R.P.: were responsible for evidence synthesis and manuscript preparation; R.P., E.O.M., and K.I.Q.: Contributed to conceptualization, analysis, and interpretation of the results, as well as review and editing of the content. All authors reviewed the results and approved the final version of the manuscript.

LIST OF ABBREVIATIONS

CDC	=	Centers for Disease Control and Prevention
EML	=	Essential Medicines List
FDA	=	Food and Drug Administration
HPAI	=	Highly Pathogenic Avian Influenza
ICU	=	Intensive Care Unit
NAI	=	Neuraminidase Inhibitor
PAHPA	=	Pandemic and All-Hazards Preparedness Act
PHEIC	=	Public Health Emergency of International Concern
QALY	=	Quality Adjusted Life Years
RCF	=	Residential Care Facility
RCT	=	Randomized Controlled Trial
WHO	=	World Health Organization
EMA	=	European Medicines Agency

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

This study was funded by the National Health Protection Office (NHPO) within the Health Service Executive, Ireland.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

The authors wish to thank Dr Rachel Kiersey, and Claire Gilbourne; Knowledge Management Officer, NHPO Research and Guideline Development Unit.

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