ORIGINAL RESEARCH ARTICLE

Drug Safety 2005; 28 (7): 633-643
0114-5916/05/0007-0633/$34.95/0

Corticosteroid-Associated Tendinopathies

An Analysis of the Published Literature and Spontaneous Pharmacovigilance Data

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Abstract

Introduction and objective: Corticosteroids may cause tendinopathies, an adverse effect that is not well known and characterised, although it was initially described more than 40 years ago. This study was conducted in order to characterise the important aspects of this adverse reaction, such as the role played by routes of corticosteroid administration, therapy duration, comedication, cumulative corticosteroid dose and underlying disease.

Study design and methods: Published case reports of tendinopathies that were associated with corticosteroid use were identified by a comprehensive literature search using the databases MEDLINE, Pharm-line, EMBASE, ToxFile, Adis Inpharma, International Pharmaceutical Abstracts, Drug Information Fulltext and PASCAL. The reference lists of all pertinent articles were cross-referenced to retrieve additional cases. Spontaneous reports were requested from the Uppsala Monitoring Centre (the WHO Collaborating Centre for International Drug Monitoring). Information of published and spontaneous reports was analysed with regard to age, sex, underlying disease, individual corticosteroids, equivalent corticosteroid dose, latency time, cumulative dose, route of administration, comedication and type of tendinopathy.

Results: We included and analysed 73 published case reports and case series involving 133 patients and 191 spontaneous reports of corticosteroid-associated tendinopathies. The proportion of women with tendinopathies was 50.8% and 41.0%, respectively. The mean age (± standard deviation) of patients with a tendinopathy was 50 ± 17 years and 61 ± 16 years, respectively. The predominant routes of administration were oral (33% of published cases and 47% of spontaneous cases) and intra-articular (35% of the published cases or parenteral (7% of the spontaneous cases). There were isolated cases of tendinopathy after inhaled or topical (i.e. ocular, cutaneous, nasal) corticosteroid use. Tendinopathies that were reported in the literature cases consisted mainly of tendon ruptures (93%), predominantly of the Achilles tendon. Of the spontaneous cases, 31% had a rupture and the remaining cases had a tendinitis or an unspecified tendon disorder.

Conclusion: Oral and parenteral applications, especially intra-articular use, were the most prevalent routes of administration in cases with corticosteroid-associated tendinopathies. However, topical application has also been rarely associated with

tendinopathies. Future pharmacoepidemiological studies should further address this issue to quantify the risk of corticosteroid-associated tendinopathies.

More than 40 years ago the first case reports linked the use of corticosteroids with the occurrence of tendinopathies, mainly tendon ruptures.[1-5] Even though numerous additional reports of tendinopathies associated with intra-articular, topical and systemic corticosteroid application have been published in the following years,[6-14] and both *in vitro* and *in vivo* studies have tried to elucidate the potential pathomechanism of the reaction,[15-20] several aspects of this adverse drug reaction have not been analysed yet and are still unclear. In this study we analysed both published and spontaneous reports of corticosteroid-associated tendinopathies in order to better characterise certain issues of this adverse corticosteroid reaction.

Methods

Published Case Reports

We performed a comprehensive literature search of the databases MEDLINE (1966–March 2003), Pharm-line (1978–March 2003), EMBASE (1974–March 2003), ToxFile (1965–March 2003), Adis Inpharma (1983–March 2003), International Pharmaceutical Abstracts (1970–March 2003), Drug Information Fulltext (2003) and PASCAL (1984–March 2003) to identify published case reports of corticosteroid-associated tendinopathies. We used the following keywords to identify relevant articles in English, French, German, Italian, Spanish, Dutch and Danish: 'corticosteroid' combined with 'tendon rupture', 'tendon injury', 'tendon disease', 'tendinopathy', 'tendinitis', 'tendon lesion' or 'tendon trauma'. The reference lists of all pertinent articles were also cross-referenced to retrieve additional cases.

We extracted the information on the age and sex of the patient, the disease/condition for which the corticosteroid therapy was prescribed (classified according to the tenth edition of the International Classification of Diseases and Related Health Problems [ICD-10]), the specific corticosteroid, the equivalent daily corticosteroid dose, the latency period between the start of corticosteroid therapy and the onset of tendinopathy, the cumulative corticosteroid dose, the route of administration, the occurrence of comedication and underlying tendon pathology. Equivalent corticosteroid doses were estimated from the relative anti-inflammatory potency of the individual corticosteroid as compared with hydrocortisone (cortisol)[21,22] and the daily individual corticosteroid dose.

Additionally, we evaluated whether an underlying disease that *per se* may be associated with tendinopathies (i.e. rheumatoid arthritis,[7,23-25] systemic lupus erythematosus,[26-29] diabetes,[30-32] primary or secondary hyperparathyroidism,[33-36] gout, [37-40] renal diseases including uraemia,[41-43] renal failure[26,44,45] and chronic haemodialysis,[45-49] or renal transplantation[43,50-52]) was mentioned in the case report/case series.

Table I. Median dose, latency period and cumulative dose for corticosteroid-induced tendinopathies associated with the two most frequent routes of administration in the published cases

Parameter	Oral corticosteroids (n = 44)	Intra-articular corticosteroids (n = 47)
Median daily dose in mg[a] (IQR)	80 (40–120) Information available from 40 patients (91%)	120 (30–240) Information available from 18 patients (38%)
Median latency period in days (IQR)	2190 (90–10 950) Information available from 37 patients (84%)	49 (3–2190) Information available from 31 patients (66%)
Median cumulative dose in g[b] (IQR)	175 (32–354) Information available from 35 patients (80%)	0.21 (0.03–0.4) Information available from 15 patients (32%)

a Relative corticosteroid potency multiplied by the daily individual corticosteroid dose = hydrocortisone (cortisol) equivalent in mg.

b Latency period (days) multiplied by the daily dose.

IQR = interquartile range.

Table II. Routes of corticosteroid administration associated with the published and spontaneous cases of tendinopathy

Route of administration	Patients in published cases (n= 133) [n (%)]	Patients in spontaneous cases (n= 191) [n (%)]
Oral	44 (33.1)	89 (46.6)
Parenteral	47 (35.3)	13 (6.8)
intra-articular	47 (35.3)	1 (0.5)
intravenous	0 (0.0)	5 (2.6)
intramuscular	0 (0.0)	4 (2.1)
intrathecal	0 (0.0)	1 (0.5)
subcutaneous	0 (0.0)	2 (1.0)
Inhalation	1 (0.8)	7 (3.7)
Topical	1 (0.8)[a]	7 (3.7)[b]
Combined	17 (12.8)	17 (8.9)
oral with intravenous	0 (0.0)	6 (3.1)
oral with intra-articular	4 (3.0)	0 (0.0)
oral with inhaled	13 (9.8)	10 (5.2)
inhaled with intramuscular	0 (0.0)	1 (0.5)
Unknown	23 (17.3)	58 (30.4)

a Cutaneous application.

b Four nasal, two ocular and one cutaneous application.

Spontaneous Pharmacovigilance Data

We requested information on cases that had been spontaneously reported to the Uppsala Monitoring Centre (UMC) [the WHO Collaborating Centre for International Drug Monitoring]. The UMC is responsible for the collection of data on adverse drug reactions from over 70 countries around the world and the detection of signals of drugs that might possibly have problematic adverse effects.

The search terms 'tendinitis', 'tendon disorder', 'tendosynovitis' or 'tendon disorder' combined with the Anatomical and Therapeutic Classification (ATC) codes for systemic or topical corticosteroids (i.e. A01AC, A07EA, C05AA, D07AA, D07AB, D07AC, D07AD, D07BA, D07BB, D07BC, D07BD, D07CA, D07CB, D07CC, D07CD, D07XA, D07XB, D07XC, D07XD, D10AA, H02AB, H02BX, M01BA, N02CB, R01AD, R03BA, S01BA, S01BB, S01CA, S01CB, S01CC, S02BA, S02CA, S03BA, S03CA) were used to identify spontaneous reports on corticosteroid-associated tendinopathies. The same information as for published cases was retrieved from spontaneous reports, where available. Information was obtained up to April 2003.

Analysis

We used descriptive statistics with means (± standard deviations) and ranges or medians with interquartile ranges to analyse the data of published and spontaneous case reports.

Results

Published Cases

From the literature we identified 73 published case reports or case series,[1-14,23-29,50-101] involving a total of 133 patients with corticosteroid-associated tendinopathy.

The mean age of the 119 patients for whom information on age was available was 50.2 ± 17.2 years (range 17–88 years); 28 patients (24%) were ≥65 years of age. Of 116 patients for whom information on sex was available, slightly more than half were female (n = 59; 50.9%).

Information on the median daily corticosteroid dose, the median latency period between the start of corticosteroid therapy and the onset of tendinopathy, and the cumulative corticosteroid dose in patients with tendinopathy associated with the two most common routes of administration (oral and intra-articular) is displayed in table I. The various routes

Table III. Individual corticosteroids associated with tendinopathies

Corticosteroid	Patients in published cases (n = 133) [n (%)]	Patients in spontaneous cases (n = 191) [n (%)]
Prednisone or prednisolone	36 (27.1)	94 (49.2)[a]
Methylprednisolone	22 (16.5)	26 (13.6)
Prednisone or prednisolone with an additional corticosteroid	17 (12.8)	24 (12.6)
Triamcinolone	16 (12.0)	10 (5.2)
Cortisone or hydrocortisone	8 (6.0)	6 (3.1)
Betamethasone	3 (6.0)	5 (2.6)
Dexamethasone	3 (6.0)	6 (3.1)
Methylprednisone	2 (1.5)	0 (0.0)
Cortisone combined with an additional corticosteroid	2 (1.5)	0 (0.0)
Methylprednisolone combined with triamcinolone	2 (1.5)	0 (0.0)
Beclometasone	0 (0.0)	4 (2.1)
Budesonide	0 (0.0)	3 (1.6)
Fluticasone propionate	0 (0.0)	3 (1.6)
Other corticosteroids	0 (0.0)	4 (2.1)
Other combinations of corticosteroids	0 (0.0)	6 (3.1)
No information	22 (16.5)	0 (0.0)

a 53 patients received prednisone (oral application in 51 patients, ocular application in 1 patient and nasal application in 1 patient) and 41 patients received prednisolone (oral application in all patients).

of administration associated with the condition are listed in table II and the individual agents implicated in each case are shown in table III. In 58 of 133 case patients (43.6%), information on comedication was available. In four patients the comedication included a quinolone antibacterial.

Table IV provides a summary of the underlying diseases for which corticosteroid therapy was used. In 55 of 133 patients (41.4%) a disease was mentioned that *per se* may induce tendinopathies. Sixteen patients (12.0%) had a renal disease (i.e. 1 patient with chronic renal failure, 15 patients with renal transplantation), 21 patients (15.8%) had systemic lupus erythematosus, 12 patients (9.0%) had (rheumatoid) arthritis, 5 patients (3.8%) had both systemic lupus erythematosus and (rheumatoid) arthritis and 1 patient (0.8%) had type 2 diabetes mellitus. In 17 patients (12.8%) where no disease that predisposes to tendinopathy was mentioned, the corticosteroid was applied for an underlying tendinopathy (i.e. 12 patients with achillodynia, 3 with tendinitis of the Achilles tendon and 1 with tenosynovitis of the tibialis anterior and 1 with tendinosis of the elbow). Fourteen patients (29.8%) who received intra-articular corticosteroids were described as 'athletes'.

The types of tendinopathies reported in the published cases are displayed in table V. Of the total 133 patients, 124 (93.2%) had a tendon rupture, of which 31% were bilateral. More than half of the published cases had a tendinopathy of the Achilles tendon, approximately 19% had a tendinopathy that affected the patellar and 8% had a tendinopathy that affected the biceps.

Of the 47 patients who received an intra-articular corticosteroid application, 45 had a complete rupture and 2 had an incomplete rupture. In 11 patients (23.4%) the rupture occurred after a single intra-articular application.

Spontaneous Cases

By April 2003 the UMC had received reports on 191 patients, with a total of 208 tendinopathies, in association with corticosteroids. The mean age of 168 patients for whom information on age was available was 60.9 ± 16.1 years (range 12–87 years of age); of those, 86 (51.2%) were ≥65 years of age.

Of 178 patients for whom information on sex was available, 73 (41.0%) were female.

Information on daily corticosteroid dose, the latency period between the start of corticosteroid therapy and the onset of tendinopathy, and the corresponding corticosteroid dose in cases with tendinopathy associated with oral or parenteral corticosteroids, is displayed in table VI. The various routes of administration associated with the condition are listed in table II and the individual agents implicated in each case are shown in table III.

In 150 patients (78.5%), information on concomitant drug use was provided; in those, a total of 373 drugs were used in addition to the corticosteroids. The predominant class of concomitant drugs were anti-infective agents (n = 143 [38.3%]), of which 123 were quinolones (mainly ciprofloxacin [n = 48], levofloxacin [n = 36] and ofloxacin [n = 17]).

Of a total of 208 tendinopathies, 60 (28.8%) were reported as ruptures, 91 (43.8%) were reported as tendinitis, 53 (25.5%) were reported as tendon disorder and 4 (1.9%) were reported as synovitis/tendosynovitis. Table VII displays the type of tendinopathy and the corresponding route of corticosteroid administration. Seven patients (3.7%) received an inhaled corticosteroid only; of those, 2 patients with a rupture received a quinolone concomitantly and of the remaining five without a rupture, one received a quinolone concomitantly.

In 82 patients, information on causality assessment was provided. The imputability that the corticosteroid was causally linked with the tendinopathy was assessed as 'possible' in 66 patients (81.5%), 'probable' in 14 patients (17.1%) and 'certain' in 2 patients (2.4%).

Discussion

The present study is the first analysis of published and spontaneous reports on corticosteroid-associated tendinopathies.

The wide age range (12–88 years) of patients with corticosteroid-associated tendinopathy who were included in the analysis indicates that patients of all ages are at risk of experiencing a corticosteroid-induced tendinopathy. Additionally, the even sex distribution, both in published and spontaneous cases, suggests a similar risk in men and women, assuming there is a comparable corticosteroid exposure prevalence.

Oral use of corticosteroids was associated with tendinopathies in approximately half of the sponta-

Table IV. Underlying diseases for which corticosteroid therapy was used[a]

Underlying disease	Patients in published cases [n (%)]
Musculoskeletal and connective tissue	76 (57.1)
systemic lupus erythematosus	21 (15.8)
(rheumatoid) arthritis	12 (9.0)
systemic lupus erythematosus + (rheumatoid) arthritis	5 (3.8)
local joint pain	18 (13.5)
tendinopathy	17 (12.8)
other musculoskeletal or connective tissue disorder	3 (2.3)
Genitourinary system	16 (12.0)
renal transplantation due to renal failure	15 (11.3)
other genitourinary system disorder	1 (0.8)
Respiratory system	20 (15.0)
chronic obstructive pulmonary disease	13 (9.8)
asthma	7 (5.3)
Skin and subcutaneous tissue (i.e. psoriasis, eczema and other skin or subcutaneous disorders)	3 (2.3)
Digestive system (i.e. Crohn's disease or ulcerative colitis)	2 (1.5)
Other	6 (4.5)
No information	10 (7.5)

a Data from the spontaneous cases has not been included as this information is either often missing or an indication is provided for a drug other than the corticosteroid.

Table V. Types of corticosteroid-associated tendinopathies in 133 published cases

Affected tendon	Total number of patients (n = 133) [n (%)]	Patients with rupture (n = 124) [n (%)][a]	Patients with bilateral rupture (n = 38) [n (%)][a]
Achilles	68 (50.1)	60 (88)	22 (37)
Patellar	25 (18.8)	25 (100)	11 (44)
Biceps	11 (8.3)	11 (100)	0 (0)
Tibialis anterior	6 (4.5)	6 (100)	0 (0)
Calcaneus	4 (3.0)	4 (100)	1 (25)
Peroneus brevis	4 (3.0)	4 (100)	2 (50)
Extensor digitorium communis	3 (2.3)	3 (100)	0 (0)
Flexor pollicis longus	3 (2.3)	3 (100)	0 (0)
Quadriceps	2 (1.5)	2 (100)	0 (0)
Extensor pollicis longus	2 (1.5)	2 (100)	1 (50)
Supraspinatus	1 (0.8)	1 (100)	0 (0)
Tibialis posterior	1 (0.8)	0 (0)	0 (0)
Triceps	1 (0.8)	1 (100)	0 (0)
Epicondylus lateralis	1 (0.8)	0 (0)	0 (0)
Achilles and patellar	1 (0.8)	1 (100)	1 (100)
Supraspinatus and biceps	1 (0.8)	1 (100)	0 (0)

a Given as a percentage of the total number of patients.

neous cases and one third of the published cases. Since we can assume that in general the exposure prevalence of oral corticosteroids exceeds the exposure prevalence of parenteral, especially intra-articular, corticosteroids we might anticipate higher relative risks in association with parenteral corticosteroids compared with oral use. Additionally, our data suggest that the latency period between the start of corticosteroid therapy and the onset of symptoms, as well as the cumulative dose required to induce a tendinopathy, is higher for oral corticosteroid use than for intra-articular use. However, since we did not perform any inferential statistical analyses, this assumption remains hypothetical.

The results from the published cases on the median time between initiating oral corticosteroid therapy and the development of tendinopathy suggests that it may take several years of oral exposure before there is a clinical effect on tendons. However, it is unclear as to how to interpret the huge difference between the median latency period in published and spontaneous cases in association with oral corticosteroids (i.e. >70 months found in published cases and 21 days in spontaneous cases). Of course, we cannot exclude that some cases that were included in the analysis of both published and spontaneous cases had a tendinopathy that was unrelated to oral corticosteroid therapy. Moreover, it can be assumed that many cases with oral corticosteroid use had an intermittent corticosteroid therapy, thereby distorting the estimate of the latency period.

In the spontaneous cases, the median latency period of 7 weeks in patients receiving corticosteroids intra-articularly is considerably shorter than the latency period found with oral corticosteroid-associated tendon disorders; moreover, almost a quarter of the published cases with a tendinopathy after intra-articular corticosteroid use had the tendon disorder after a single application.

Whether the risk of tendinopathy between different corticosteroids differs cannot be answered by this kind of analysis. It is hard to differentiate whether the frequency of reporting tendinopathies with different corticosteroids is associated with the exposure prevalence to individual corticosteroids or, in fact, points to differences in the individual potential to cause tendon disorders.

Interestingly, there were some published reports as well as spontaneous reports of corticosteroid-associated tendinopathies in patients using only inhaled or topically applied corticosteroids. Whether those tendon disorders were indeed causally linked to inhaled or topical corticosteroid use cannot be answered with certainty. However, both inhaled and

topical corticosteroid use is associated with the typical systemic adverse effects that are known from oral or parenteral corticosteroid use, such as hypothalamic-pituitary-adrenal axis suppression,[102-104] cataract[105-107] or changes of bone mineral density and bone fractures.[108-111]

The present study has several limitations, of which many are related to the peculiarities of spontaneous reports of adverse drug reactions, namely reporting and selection bias, as well as the quality of the information. Since there is a reporting bias with regard to severity of a potential adverse drug reaction, it is likely that tendon ruptures are over represented in the published cases since almost 93% of the published corticosteroid-associated tendinopathies were ruptures. This means that the data of published cases would reflect features of corticosteroid-associated ruptures, but not necessarily tendinopathies in general. This assumption is further underlined by the fact that ruptures made up less than a third (31%) of the spontaneous cases; whether this number still over represents the 'true' proportion of ruptures in corticosteroid-associated tendinopathies overall is unclear. Of course, the problem of reporting bias also affects the data obtained from the spontaneous cases. Because of a probable reporting bias with regard to severity, it can be assumed that tendinopathies of minor or moderate severity are very likely to be relevantly under-represented in our analysis. Additionally, we cannot exclude with certainty that there are not some duplicates between the published and the spontaneous cases.

Interestingly, the prevalence of corticosteroid-associated tendinopathies in published cases was highest in the Achilles and patellar tendons and accounted for almost 70% of all cases. When healthy, both types of tendons require massive forces to be disrupted and both can be weakened through certain systemic disease processes, corticosteroids and fluoroquinolones. The vast majority, both in cases with Achilles and patellar tendinopathy, were reported to have a rupture (88% and 100%, respectively). However, Achilles tendinopathy especially can also affect inactive and older people, which is not seen in most other tendons. Therefore, a sedentary lifestyle or advanced age could bias the results.

Furthermore, in both published and spontaneous cases, important information such as the use of other drugs was inadequately reported or not reported at all. This makes it very difficult to assess a causal relationship between corticosteroid exposure and the occurrence of a tendinopathy. Therefore, there is a risk that some reports of tendinopathy included in our analysis might, in fact, be unrelated to corticosteroid use. Moreover, it is very difficult to assess the impact of the comedication that was concomitantly used with the corticosteroids. For instance, in spontaneous cases >60% of patients concomitantly received quinolones, which themselves are well known to cause tendinopathies.[100,112-117] Whether, in fact, the corticosteroids alone or rather the quinolones or a combination of both were more likely to cause the tendinopathies in those cases, is unclear. As was recently shown, the risk of Achilles tendon rupture in association with quinolone use is highly increased in those patients receiving concomitant oral corticosteroids.[118]

Although we did a comprehensive search on the most important literature databases and included case reports in eight different languages, we cannot exclude that, nonetheless, some case reports were

Table VI. Median dose, latency period and cumulative dose for corticosteroid-induced tendinopathies associated with the two most frequent routes of administration in the spontaneous cases.

Parameter	Oral corticosteroid (n = 89)	Parenteral corticosteroids (n = 13)
Median daily dose in mg[a] (IQR)	80 (40–160) Information available from 60 patients (67%)	200 (120–300) Information available from 5 patients (38%)
Median latency period in days (IQR)	21 (5.5–53.5) Information available from 37 patients (84%)	3 (1–10) Information available from 10 patients (77%)
Median cumulative dose in g[b] (IQR)	2.9 (1.0–7.8) Information available from 35 patients (80%)	1.1 (0.2–1.5) Information available from 5 patients (38%)

a Relative corticosteroid potency multiplied by the daily individual corticosteroid dose = equivalent in mg hydrocortisone (cortisol).

b Latency period (days) multiplied by the daily dose.

IQR = interquartile range.

Table VII. Main tendinopathies and route of corticosteroid application in 191 spontaneous case reports with corticosteroid-associated tendinopathies

Route of administration	Rupture (n = 60) [n (%)]	Tendinitis (n = 91) [n (%)]	Tendon disorder (n = 53) [n (%)]
Oral	31 (52)	42 (46)	25 (47)
Parenteral	2 (3)	7 (8)	4 (8)
Inhaled	2 (3)	3 (3)	2 (4)
Topical (nasal, ocular, cutaneous)	1 (2)	5 (5)	2 (4)
Oral and inhaled	5 (8)	3 (3)	2 (4)
Oral and parenteral	1 (2)	3 (3)	2 (4)
Other	1 (2)	5 (5)	1 (2)
No information	17 (28)	23 (25)	15 (28)

missed and, therefore, not included in the analysis. However, we believe that this would not materially change our main results. And finally, a variety of different diseases such as rheumatoid arthritis,[7,23-25,40,71,89] systemic lupus erythematosus,[4,26-29,61,65,70,77,85] primary or secondary hyperparathyroidism,[26,33-36,119] gout,[37-40,120-122] renal diseases including uraemia,[41-43] renal failure[26,44,45,123,124] and chronic haemodialysis,[45-49,125,126] and renal transplantation[43,50-52] have been associated with tendinopathies at different sites. For some of those diseases corticosteroids are an important treatment option. Therefore, it is very difficult to assess a causal association between corticosteroid exposure and tendinopathy considering that spontaneous ruptures of tendons may be part of the features of those diseases. In a least 41% of the published cases, we found some information on an underlying disease that *per se* can predispose to tendinopathy, which may imply some sort of confounding by indication.

Conclusion

In conclusion, our analysis underlines that both oral and parenteral corticosteroid use is associated with different types of tendon disorders. There is some evidence that inhaled or topically applied corticosteroids may also be associated with tendinopathies. Therefore, pharmacoepidemiological studies would be necessary to better quantify the risk of corticosteroid-associated tendinopathy. This would help to explore not only the association of systemically applied corticosteroids with the occurrence of tendon disorders, but the potential association of topically applied corticosteroids and tendinopathies in particular.

Acknowledgements

We are grateful to Dr Peter Wolf for the comprehensive literature search. We would also like to thank Mrs Erica Walette of the Uppsala Monitoring Centre of the WHO, Uppsala, Sweden for providing the information on spontaneous pharmacovigilance data.

The information obtained from the WHO is not homogenous, at least with respect to origin or likelihood that the pharmaceutical product caused the adverse reaction. The opinions expressed in this article are those of the authors and do not represent the opinion of the WHO.

No sources of funding were used to assist in the preparation of this study. The authors have no conflicts of interest that are directly relevant to the content of this study

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