

Registered clinical evidence for ivermectin as a preventive antiviral: a landscape analysis of trials and the case for a nasally applied semisolid formulation

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Abstract

Purpose

Randomised trials of oral ivermectin have not shown benefit against COVID-19. The explanation most often advanced is pharmacokinetic: concentrations achievable at the respiratory epithelium after oral dosing fall well below those at which antiviral activity is seen in cell culture. If so, local application to the site of initial viral replication is a hypothesis oral trials cannot test. We characterised the registered evidence base to ask whether it has been evaluated.

Methods

We analysed all 253 ClinicalTrials.gov records for the intervention term “ivermectin”, then repeated the analysis against the WHO ICTRP to test dependence on a single registry. We derived indication, purpose and prophylactic intent from registry fields. Because automated inference misattributes a nasal route to records whose nasally applied agent is a different substance, we adjudicated the route of ivermectin administration at record level.

Results

Viral indications accounted for 97 of 253 ClinicalTrials.gov records (38.3%), of which 93 concerned COVID-19. Fourteen (5.5%) were adjudicated as primary prophylaxis of infection acquisition, none delivering ivermectin to the respiratory mucosa. Five gave ivermectin nasally or by inhalation (planned n = 467); all carried the status unknown, none posted results, none had a preventive objective, and no record described a semisolid nasal dosage form. Results were posted for 16 of 97 viral-indication studies (16.5%), against 30 of 129 (23.3%) for parasitic indications. ICTRP added 184 records from fourteen further registries, a combined corpus of 437 with 173 viral-indication and 28 prophylaxis studies. All 14 additional prophylaxis studies gave ivermectin orally; none administered it nasally.

Conclusion

These data do not establish that ivermectin prevents viral infection; they establish, across two registries, that the local-delivery hypothesis is untested. A nasal semisolid is a legitimate object of early-phase investigation, provided epithelial-model activity and adequate target-site exposure are shown before any efficacy claim.

Introduction

Ivermectin is a semisynthetic macrocyclic lactone derived from avermectin B1, licensed for onchocerciasis, strongyloidiasis and several other parasitic indications, and included on the WHO Model

List of Essential Medicines. Its safety record after four decades of mass administration is well characterised, and it is available at low cost in most jurisdictions. These properties made it an attractive repurposing candidate when Caly et al¹ reported that a single addition of ivermectin to SARS-CoV-2-infected Vero/hSLAM cells produced an approximately 5000-fold reduction in viral RNA at 48 h. That report was followed by an unusually large and rapid wave of clinical registration.

The pharmacokinetic objection to this repurposing effort was raised almost immediately and has not been satisfactorily answered. Schmith et al² noted that the concentration producing 50% inhibition in the Caly experiments, 2 µM, exceeded the maximum plasma concentration achievable after the approved 200 µg/kg oral dose by more than 35-fold. Using a population pharmacokinetic model and the lung-to-plasma ratio reported in cattle, they predicted that lung concentrations would remain below the in vitro IC50 even at ten times the approved dose. Their conclusion was explicit: the probability of a successful clinical trial at approved oral doses was low.

Subsequent trial results are consistent with that prediction. In the TOGETHER platform trial, 679 outpatients receiving 400 µg/kg daily for three days showed no benefit over placebo for the composite of COVID-19 hospitalisation or prolonged emergency observation (relative risk 0.90; 95% Bayesian credible interval 0.70 to 1.16), and no benefit was observed in the subgroup treated within three days of symptom onset.³ The ACTIV-6 platform reported null findings first at 400 µg/kg for three days⁴ and subsequently at a maximum targeted dose of 600 µg/kg for six days;⁵ the second result is important because it addresses directly the argument that earlier trials were underdosed. The PRINCIPLE platform, an open, randomised, adaptive trial conducted in the community, likewise reported no benefit on its primary outcomes.⁶ Recent syntheses reach compatible conclusions. The Cochrane review of ivermectin for preventing and treating COVID-19 concluded that the reliable evidence available does not support its use for either purpose outside well-designed randomised trials, and reported low- to high-certainty evidence of no beneficial effect in outpatients.⁷ Satyam et al⁸ pooled 23 randomised trials and found no significant effect on viral clearance, hospitalisation duration or symptom resolution, and Sai Yengu et al,⁹ covering 33 studies, reported no significant effect on survival.

Evidence bearing specifically on prevention is thinner. Wang et al¹⁰ identified only four prophylaxis trials among 40 randomised trials searched to October 2025, comprising 1,190 ivermectin recipients and 1,109 controls at daily doses of 0.2–0.6 mg/kg. The pooled risk ratio for SARS-CoV-2 infection was 0.37 (95% CI 0.12–1.20), a numerically favourable point estimate whose confidence interval crosses unity and which is accompanied by heterogeneity of $I^2 = 96\%$. All four contributing trials were published in 2021–2022. The single prophylaxis trial published since, a fully remote pilot of a single 200 µg/kg oral dose given within 72 h of close contact, had a null primary endpoint (adjusted absolute difference – 0.051; 95% CI – 0.26 to 0.16; $p = 0.63$) on 68 analysed participants.¹¹ Secondary signals in that trial, including a longer interval from contact to first positive test among converters, rest on 22 events and are appropriately described as hypothesis-generating.

Mechanistic confidence has also weakened. Eastman et al¹² attribute the in vitro antiviral activity to non-specific membrane perturbation and assay interference, not to any specific antiviral target.

Independently, Dinesh Kumar et al¹³ reported that ivermectin and the related compound moxidectin inhibited SARS-CoV-2 replication in Vero E6 cells but failed to do so in human primary bronchial epithelial cells at concentrations up to 10 µM, and concluded that neither higher dosing nor substitution within the compound class was likely to be useful in humans. Anyone arguing for continued investigation must do so knowing that both the clinical and the mechanistic evidence have moved against it.

There is nonetheless a narrower argument that the accumulated trial evidence does not address. Every adequately powered trial cited above administered ivermectin systemically. If what limits the drug is the concentration achievable at the respiratory epithelium, not the intrinsic activity of the molecule, then systemic administration tests a compound-plus-route combination, and a negative result constrains that combination, not the compound alone. Single-cell transcriptomic analysis has shown that the SARS-CoV-2 entry factors ACE2 and TMPRSS2 are most highly expressed in nasal epithelial cells, particularly goblet and ciliated cells, and the authors of that work noted explicitly that intranasally administered agents could therefore be effective in limiting spread.¹⁴ The nasal cavity is thus both the earliest accessible replication site and a plausible target for a locally acting prophylactic. Topical application decouples target-site concentration from systemic exposure, in principle permitting local concentrations orders of magnitude above those attainable in plasma without a corresponding increase in systemic dose. Ivermectin is already used topically at 1% for facial rosacea, so cutaneous tolerability at that concentration is established, although cutaneous and nasal mucosal tolerability are not interchangeable.

The formulation constraint on this approach is well defined. Nasal mucociliary clearance removes conventional liquid formulations rapidly, with a clearance half-life for ordinary preparations on the order of fifteen minutes;¹⁵ solutions, drops and simple sprays are a poor match for an application whose value depends on holding the mucosal surface between exposures. Mucoadhesive and semisolid systems are the established response to this constraint, prolonging residence through interaction with the mucus layer and, in some cases, through modulation of ciliary beat frequency, a mechanism that itself requires safety evaluation.^{15,16} A semisolid ointment base is additionally well suited to a highly lipophilic, poorly water-soluble molecule for which aqueous formulation is difficult.

A locally applied nasal prophylactic against respiratory viruses is not, then, a new idea; several products have already reached clinical testing. Their record is worth setting out, because it establishes both what is plausible and what is absent.

The most extensively studied agent is iota-carrageenan, a sulfated polysaccharide from red seaweed that acts by binding viral particles at the mucosal surface and impeding their entry into cells. Its record in treatment is mixed. Early exploratory work reported reductions in cold symptoms and nasal viral load,¹⁷ and a later trial in 211 patients found a shortened illness.¹⁸ The larger ICICC trial, however, missed its primary endpoint, showing only a non-significant trend in favour of the active spray, with significant differences confined to exploratory analyses of the first four days.¹⁹ In prophylaxis, the relevant study is

a pragmatic randomised, double-blind, placebo-controlled trial in Argentinian hospital personnel caring for COVID-19 patients, in which 394 participants received four daily doses of iota-carrageenan spray or placebo for 21 days. COVID-19 developed in 2 of 196 participants (1.0%) receiving carrageenan and 10 of 198 (5.0%) receiving placebo, a relative risk reduction of 79.8% (95% CI 5.3 to 95.4; $p = 0.03$) with an absolute risk reduction of 4% (95% CI 0.6 to 7.4).²⁰ The point estimate is large, but it rests on twelve events in total, the confidence interval is correspondingly wide, and the authors describe the study as a pilot requiring replication. Notably, the same agent appears in two of the registered ivermectin studies analysed below, where it was the nasally applied component of a combination whose ivermectin was given by mouth.

Azelastine, an antihistamine long marketed for allergic rhinitis, has been repurposed on the basis of in vitro antiviral activity. After earlier work suggesting accelerated reduction of nasal viral load in established infection,²¹ a phase 2 double-blind, placebo-controlled trial randomised 450 healthy adults to azelastine 0.1% nasal spray or placebo three times daily for 56 days. PCR-confirmed SARS-CoV-2 infection occurred in 5 of 227 participants (2.2%) receiving azelastine and 15 of 223 (6.7%) receiving placebo (odds ratio 0.31, 95% CI 0.11 to 0.87), with a longer mean interval to infection among those who became infected.²² This is currently the strongest prospective evidence for any nasally applied pharmacological prophylactic against SARS-CoV-2, and it too is limited: a single centre, twenty events, and an explicit call from its authors for multicentre confirmation.

Two further approaches illustrate the range of mechanisms under investigation. A nitric oxide releasing nasal spray has been evaluated principally as a treatment, where a phase 3 trial reported accelerated clearance of nasal SARS-CoV-2 RNA;²³ its prophylactic evidence is weaker and derives largely from non-randomised sources. Astodrimer sodium is a dendrimer meant to act as a physical and virucidal barrier on the mucosa. Formulated as a 1% nasal spray, it proved safe, well tolerated and not systemically absorbed in 40 healthy volunteers who applied it four times daily for 14 days,²⁴ and later work found no impairment of mucociliary function in human nasal epithelium. Efficacy against infection has not been shown.

There is no pharmaceutical obstacle to nasal semisolids as such. Mupirocin calcium 2% nasal ointment, formulated in a paraffin-based vehicle and applied to the anterior nares twice daily for five days, has been licensed for decades for eradication of nasal carriage of *Staphylococcus aureus*, principally methicillin-resistant strains, in patients and healthcare workers during institutional outbreaks. It establishes that a semisolid can be manufactured, packaged in unit-dose form, applied reproducibly to the nasal vestibule and tolerated over a course of treatment. It is an antibacterial rather than an antiviral, and its labelling states explicitly that the available data are insufficient to recommend it for general prophylaxis of infection, so it is a precedent for the dosage form and not for the indication.²⁵ On the antiviral side, nasal semisolids do exist, as the next paragraphs set out, but the formulations under active preclinical development remain at an early stage; an ion-activated gel containing 18 β -glycyrrhetic acid with activity against respiratory syncytial virus in cell culture is a recent example.²⁶

One further group of products must be considered, and it is the most directly relevant of all, because a nasally applied antiviral intended for prophylaxis of respiratory infection is not a hypothetical proposition in this region but an established commercial category. Two preparations define that category, and they differ in dosage form in a way that bears directly on the argument made here.

The first is oxolinic ointment 0.25% (oxolin, dioxotetrahydroxytetrahydronaphthalene), a non-prescription antiviral containing oxolin 2.5 mg/g in a base of mineral oil and white soft paraffin and currently registered in Ukraine under more than one marketing authorisation held by domestic manufacturers. Its labelled indications are individual prophylaxis of influenza during an epidemic period and treatment of viral rhinitis and rhinoconjunctivitis; for prophylaxis the current labelling directs application to the nasal mucosa morning and evening, with a further application immediately before anticipated contact with an infected person, and specifies no fixed duration of use²⁷. The second is recombinant interferon alfa-2b, supplied as nasal drops and as a metered nasal spray, each containing not less than 100,000 IU/mL and each available without prescription; its labelled indications include prophylaxis of respiratory viral infection after contact with a case or on chilling and during a seasonal rise in incidence, as well as treatment at the first signs of illness²⁸. The two therefore occupy different dosage-form categories, and the difference matters here: the interferon preparations are liquids — the spray is formulated with hypromellose, but neither presentation is a semisolid — so the residence-time constraint set out above applies to them substantially. Work directed at that constraint has been reported for this agent: a thixotropic sol–gel nasal spray of interferon alfa-2b, which reverts to a gel on the mucosa after spraying, has been evaluated preclinically against the marketed spray; in rats, interferon recovered from nasal washings four hours after a single administration was approximately fourfold higher for the gel than for the conventional spray (39.4 ± 4.9 versus 10.6 ± 1.0 IU/mL), although that comparison is preclinical and concerns residence rather than clinical effect.²⁹ The oxolinic ointment, by contrast, establishes that a nasally applied antiviral semisolid can be manufactured, packaged, distributed and sold at low cost in this region, which removes much of the uncertainty that would otherwise attach to manufacturability, packaging and application of the product proposed here.

The evidentiary position of these products is, however, the opposite of their commercial position, and the contrast is what makes them worth describing. The clinical studies supporting oxolin date from 1970, and investigators who went looking could not locate their full texts in any electronic database. The only modern synthesis is an unrefereed preprint pooling four Soviet trials of more than ten thousand subjects, identified from review articles instead of the primary reports, which yielded a relative risk for influenza morbidity of 0.60 (95% CI 0.49 to 0.74).³⁰ The authors of that analysis are explicit that no full-text clinical study was retrievable. Oxolin is not registered in the European Union or the United States, and it does not appear in the most recent evidence synthesis of antiviral prophylaxis of influenza known to us: the network meta-analysis conducted to support the update of the WHO influenza guidelines screened 11,845 records and included 33 randomised trials of six antivirals — zanamivir, oseltamivir, laninamivir, baloxavir, amantadine and rimantadine — among which oxolin is not represented.³¹ That absence reflects the restriction of the review to approved antivirals as much as the inaccessibility of the primary

studies, and it should not be read as a negative finding about the compound. We identified no contemporary randomised evidence for the nasal interferon alfa-2b preparations marketed here in the prophylactic indication either. Decades of routine use across this category have produced a body of evidence that cannot now be appraised, replicated or, in any meaningful sense, believed or disbelieved.

That last statement requires an important qualification, because the active principle of the interferon preparations has in fact been tested rigorously, though at different products and at doses one to two orders of magnitude above those the marketed nasal preparations deliver. Intranasal recombinant interferon alfa was evaluated as a spray in properly conducted randomised, placebo-controlled trials in the 1980s, and it worked. In a family-contact study of 120 adults using 325 courses of 5 million IU applied daily for seven days, participants exposed to rhinovirus experienced 76% fewer symptom days and 86% fewer definite illnesses than placebo recipients, although the benefit was confined to rhinovirus and was not demonstrated for influenza A or B or for coronavirus 229E³². A companion trial reached compatible conclusions³³, and in a seasonal-prophylaxis study of 304 working adults receiving 10⁷ IU daily, rhinovirus-associated respiratory illness occurred in 13 of the placebo recipients (8.5%) and in none of the interferon recipients ($p = 0.0002$)³⁴.

The reason this approach was nonetheless abandoned is the single most instructive fact in the present literature for anyone proposing a nasal prophylactic. Prolonged administration was not tolerated. In the seasonal-prophylaxis trial, nasal irritation — obstruction, discomfort, blood-tinged mucus, punctate bleeding sites, erosions and superficial ulcerations — occurred in 40 interferon recipients by the third week of treatment ($p < 0.0001$ versus placebo), and the frequency of nasal symptoms and the overall rate of respiratory illness were significantly higher in interferon recipients during weeks two and three³⁴. So an intranasal antiviral prophylactic that worked was abandoned — not because it failed to prevent infection, but because the nasal mucosa would not tolerate the course of treatment it required.

Three conclusions follow, and they pull in different directions. The first encourages the general strategy: agents acting locally in the nasal cavity, by mechanisms as different as viral capture, receptor interference, chemical inactivation and innate immune induction, have produced measurable reductions in infection in prospective trials, and the premise that the nasal mucosa is a tractable prophylactic target does not need to be argued from first principles. The second concerns the dosage form, which in this setting is neither novel nor speculative. Mupirocin establishes it for an antibacterial indication in international practice, and oxolinic ointment establishes it for an antiviral indication in regional practice, which removes much of the uncertainty that would otherwise attach to manufacturability, regulatory precedent, patient acceptability and adherence over a multi-week prophylactic course.

The third is a caution, and the sharpest of them. The semisolid nasal antiviral form is occupied but unevidenced: every product for which a contemporary controlled trial exists is a spray or a solution, and the semisolid preparation in routine preventive use rests on data that cannot now be retrieved. These products are thus not merely precedents for the proposal made here but warnings about it, showing how nasal antiviral semisolids can enter and remain in widespread use for decades without ever generating

evidence adequate to establish whether they work. That is a failure to which a low-cost, familiar, over-the-counter preventive product in this therapeutic category is evidently prone. The interferon experience adds a second and more specific warning: tolerability of the nasal mucosa over a multi-week course, rather than efficacy, is what defeated the last intranasal prophylactic to reach this stage, and a semisolid intended for prolonged residence has every reason to be examined on that endpoint first. Figure 1 sets out this landscape by dosage form and mechanism, and locates the position the proposed product would occupy.

A final qualification should be entered before this comparison is pressed too far. Carrageenan and astodimer act extracellularly, capturing or inactivating virions before they reach the epithelium, and their efficacy depends only on the drug being present on the mucosal surface. Ivermectin's proposed mechanism is intracellular, so a nasal formulation would have to do more than coat the surface: it would have to reach a sufficient concentration inside epithelial cells. The barrier agents establish that the anatomical target is accessible; they do not establish that a compound acting inside the cell can reach an effective concentration there, and that question is the one the development pathway proposed below is designed to answer.

The burden such a product would address is substantial and, in the setting in which the present work is conducted, has been quantified by national surveillance. Ukraine operates universal notification of acute respiratory infection (ARI) alongside sentinel influenza-like illness and severe acute respiratory infection surveillance, so national case counts are available for most of the past decade, although with important qualifications set out below. Selected season-level figures are summarised in Table 1, and Fig. 1 shows the changing virological composition of recent seasons.

Table 1

Reported burden of influenza and other acute respiratory infections in Ukraine, selected seasons.

Season	Reported burden	Virological and mortality notes
2014/2015	Peak weekly ARI incidence 700.5 per 100,000 (week 9/2015)	11 laboratory-confirmed influenza deaths
2015/2016	Peak weekly ARI incidence 1,036.6 per 100,000 (week 4/2016); 4,035,623 ARI cases to week 7/2016, approximately 9% of the population	A(H1N1)pdm09 predominant; 342 laboratory-confirmed influenza deaths
2022/2023	2,190,796 cases (5.3% of the population) from 3 October 2022 to 12 February 2023, 58.0% fewer than the corresponding period of 2021/2022	14 PCR-confirmed influenza deaths, against none recorded in 2021/2022
2023/2024	4.8 million cases; 13,391.1 per 100,000, 22.7% above the preceding season; peak weekly incidence 645.0 per 100,000 (week 6/2024)	17,636 registered influenza cases (0.36% of ARI); 72 influenza deaths; influenza viruses 49.8% of respiratory viruses detected; SARS-CoV-2 share fell from 31.6% to 14.9%, RSV rose from 19.0% to 25.6%
2025/2026	4,236,118 cases; 11,928.2 per 100,000, 7.1% below the preceding season; 11.9% of the population sought medical care; peak weekly incidence 508.9 per 100,000 (week 8/2026); 119,799 hospitalisations (2.8% of cases)	A(H3) predominant (71% of characterised influenza viruses), A(H1)pdm09 28%, B/Victoria about 1%; 201 ARI-associated deaths, comprising 86 from influenza and other ARI and 115 among people with laboratory-confirmed COVID-19

Sources: 2014/2015 and 2015/2016 from Newitt et al;³⁶ 2022/2023 and 2025/2026 from the Center for Public Health of the Ministry of Health of Ukraine;³⁷ 2023/2024 from Zadorozhna et al.³⁵ Seasons 2016/2017 to 2021/2022 are not tabulated because comparable published national season-level figures were not retrieved for this analysis.

Three features of these data bear on the case for a prophylactic. First, the scale is large and persistent: in each of the two most recently reported full seasons, between 11.9% and roughly 13% of the population presented to health services with a respiratory infection, and the peak weekly incidence exceeded the national epidemic threshold of 480 per 100,000. Second, the aetiology is polymicrobial and shifts between seasons. In 2023/2024 influenza viruses accounted for 49.8% of respiratory viruses detected while the share of SARS-CoV-2 fell by more than half and that of RSV rose; by 2025/2026 A(H3) predominated among influenza viruses and COVID-19 constituted only 0.5% of registered ARI cases. An intervention acting at the mucosal surface, not on a specific viral target, would in principle be indifferent to this turnover, which is one of the arguments advanced for the barrier agents discussed above. Third, access to influenza vaccination in Ukraine is constrained by the way it is financed. Influenza vaccination is provided for in the Calendar of Prophylactic Vaccinations, but not in its age-based schedule of mandatory childhood immunisation. It appears in the chapter on vaccination by state of health, where annual vaccination from six months of age is specified for a defined list of conditions carrying a high risk

of complications, among the recommended vaccinations for occupational and risk groups, persons over 60 years, and pregnant women, and among vaccinations given on epidemic indications.³⁸ In practice a person seeking influenza vaccination consults a family physician and buys the vaccine in a pharmacy; employers may arrange vaccination for their staff and local authorities may provide it for vulnerable groups, and for the 2025/2026 season the Public Health Center and the Ministry of Health obtained 20,000 doses of a quadrivalent vaccine as humanitarian aid for health workers.³⁹ Vaccine against COVID-19, by contrast, is procured centrally and distributed through the health service. The resulting coverage is low: across the whole 2025/2026 season 78,904 people in Ukraine were vaccinated against influenza, of whom 44,582 belonged to medical or epidemiological risk groups and 20,375 were staff of healthcare facilities.⁴⁰ In the 2023/2024 season, of the 72 deaths from influenza reported for that season, none occurred in a person vaccinated against either influenza or COVID-19.³⁵ A low-cost, self-administered, non-vaccine preventive measure would occupy a real gap in this setting, which is a large part of the practical motivation for the present analysis.

These figures require careful qualification and should not be read as incidence of infection. Universal ARI notification in Ukraine records clinically diagnosed cases, the great majority of which are never laboratory-tested; the discrepancy is stark in 2023/2024, when influenza was registered as the diagnosis in 0.36% of ARI cases while accounting for 49.8% of respiratory viruses identified under sentinel surveillance. Registered influenza case counts, and the case-fatality figures derived from them, tell us more about diagnostic practice than about viral epidemiology. Since 2022, reporting has been incomplete in areas affected by hostilities: Zadorozhna et al³⁵ recorded substantially lower registered ARI incidence in those oblasts, with zero reporting from Luhansk oblast, and noted that incidence is calculated against pre-war denominators while the resident population has changed considerably. Season-to-season comparisons across the 2022 boundary are consequently unreliable, and the apparent 58.0% fall in 2022/2023 should be interpreted as reflecting surveillance disruption and population displacement at least as much as reduced transmission. The COVID-19 pandemic period introduces a further discontinuity, since non-pharmaceutical interventions suppressed circulation of the other respiratory viruses and the B/Yamagata lineage has not been detected anywhere since 2020.

Before such a product can be justified, it is necessary to establish what has in fact been tested. Narrative accounts of the ivermectin literature have concentrated on the efficacy of oral treatment; the distribution of registered studies across indications, routes and preventive versus therapeutic intent has not, to our knowledge, been characterised systematically. The present analysis addresses that question using the full set of records returned by ClinicalTrials.gov, with the specific aim of determining whether the local-delivery hypothesis has been evaluated and, if not, what an appropriate development pathway would require.

Materials and Methods

Data source and retrieval

We obtained study records from ClinicalTrials.gov, the registry maintained by the U.S. National Library of Medicine,⁴¹ for the intervention term “ivermectin”. We used two comma-separated export files: a study-record file containing 253 records with seventeen fields, and a study-documents file containing 253 corresponding records with four fields. We joined the two files on the NCT Number field; the join was complete, with all 253 records matched. The retrieved fields were NCT Number, Study Title, Study URL, Study Status, Brief Summary, Study Results, Conditions, Interventions, Sex, Age, Phases, Enrollment, Study Type, Study Design, Primary Completion Date, Completion Date, Locations and Study Documents. We provide the complete extracted dataset as Table S2.

To establish whether our findings were an artefact of relying on a single registry, we repeated the analysis against the WHO International Clinical Trials Registry Platform (ICTRP)⁴², which aggregates records from national and regional registries worldwide. We searched the ICTRP Search Portal on the intervention term “ivermectin” and exported the results as CSV. Five rows contained stray delimiters within long free-text fields; we repaired these by merging the surplus fields back into the final text column instead of discarding them, so that all retrieved records were retained. Because ICTRP indexes ClinicalTrials.gov, we partitioned records by identifier and treated only those held in other registries as additions. We then applied the same derivation and adjudication rules to that subset: indication category, automated route inference, record-level adjudication of the route of ivermectin administration, and manual adjudication of prophylactic intent. We document provenance, procedure and limitations for this step in Table S14. We also searched the same portal separately for abamectin, moxidectin, eprinomectin, doramectin and selamectin.

The ClinicalTrials.gov export is dated 31 August 2026 and the WHO ICTRP export 3 September 2026. Registry contents change continuously, so all counts we report are specific to those two snapshots.

Derived variables

We derived five variables from the retrieved fields: indication category, an automated inference of administration route, an adjudicated route of ivermectin administration, study purpose, and prophylactic intent. Their definitions, together with the exact rules applied, are given in Table S1.

Indication category. We assigned records to one of five categories by keyword matching against the Conditions field: viral infection, parasitic or vector-borne disease, dermatological (non-parasitic), oncological, or other and pharmacological. Where the Conditions field was uninformative we used the Study Title, Interventions and Brief Summary fields. We gave precedence to the viral category, so that records naming both a viral and a non-viral condition were classified as viral. This choice is conservative with respect to the present analysis, since it inflates rather than deflates the apparent volume of antiviral investigation.

Administration route. Route is not a structured field in the retrieved export, so we first inferred it automatically from the concatenated Title, Interventions and Brief Summary text. Where no route term

was present, we labelled the record “not stated in retrieved fields” and did not impute the oral route. This matters for interpretation. Oral administration is the default for licensed systemic ivermectin, but imputing it would have turned an absence of documentation into a positive finding. We recorded multiple routes where more than one was described, so route categories are not mutually exclusive.

Automated inference of this kind is unreliable for the specific question at issue here, because it attributes a route to a record whenever a route term appears anywhere in its free text. We identified three failure modes. The inference attributed a nasal route to records in which the nasally applied agent was a different substance, specifically iota-carrageenan; to records where the word referred to nasopharyngeal specimen collection, not administration; and to a record in which ivermectin was not an intervention at all. We therefore read individually every record for which the automated inference implied a mucosal or ophthalmic route, and constructed a second variable, the adjudicated route of ivermectin administration. We reassigned fourteen records; each reassignment and its reason are listed in Table S13. The consequence is material: automated inference flags ten records as nasal, but only four in fact administer ivermectin that way. All route analyses we report below use the adjudicated variable, and we retain the automated inference in Table S2 solely so that readers can inspect the difference between the two.

The Interventions field does not name ivermectin in 42 of the 253 records. In most the drug is identifiable elsewhere in the record, appears under a code name, or is embedded in a combination or bioequivalence arm; in two records, identified in Table S13, ivermectin is not an intervention and the record was returned for contextual reasons.

Study purpose. We extracted the Primary Purpose value verbatim from the Study Design string, together with Allocation and Masking.

Prophylactic intent. Registry Primary Purpose values proved insufficient here. Studies aimed at preventing progression or hospitalisation among already-infected participants are often described in language indistinguishable from that used for prevention of infection. We therefore adjudicated each candidate record manually against a single pre-specified criterion: a study qualifies as primary prophylaxis only where its stated objective is prevention of infection in uninfected persons, whether pre-exposure or post-exposure. We classified as treatment those studies whose stated objective is prevention of progression, complications or hospitalisation in infected persons. Twenty-one records matched the initial automated screen; fourteen satisfied the adjudication criterion. The seven excluded records and the basis for their exclusion are identifiable from Table S4.

Analysis

Our analysis was descriptive. We computed counts, proportions, medians and interquartile ranges in Python 3 using the pandas library, and generated the supplementary workbook with openpyxl. We applied no inferential statistics and attempted no meta-analysis. Two considerations preclude quantitative synthesis: registry records do not contain outcome data for the great majority of the corpus,

and the heterogeneity of the underlying trials in dose, population, endpoint and epidemiological context is such that pooling would not yield an interpretable estimate.

We report enrolment figures as supplied. The export does not separate actual enrolment in completed studies from anticipated enrolment in ongoing, withdrawn or unknown-status ones, so aggregate totals describe planned, not achieved, exposure.

Scope and reporting conventions

This is a cross-sectional, registry-based meta-research study: our units of analysis are registered study records, not patients, and we are asking about the composition of a research literature, not the effect of an intervention. It is not a systematic review of clinical outcomes. We conducted no literature search beyond the two registries for the purpose of enumeration, applied no risk-of-bias instrument, and undertook no PRISMA-conformant search of bibliographic databases; accordingly, we make no claim of systematic-review status. Design attributes reported in the Results are transcribed from registry fields and represent what investigators declared at registration, not an independent methodological appraisal. Where we refer to trial results in the Discussion, we draw these from the published sources cited and not from the registry exports. No reporting guideline fits this design exactly. STROBE for cross-sectional studies is the closest instrument, and we have followed its descriptive elements — setting, data sources, variables, statistical methods, descriptive data and limitations — wherever they apply to records rather than participants.

Results

Composition of the registered evidence base

The 253 retrieved records comprised 229 interventional and 24 observational studies, with a combined planned enrolment of 846,268 participants. Their distribution across indication categories is given in Table 2 and, in full, in Table S3; Fig. 2 summarises the composition of the corpus across both registry sources and the successive narrowing from the full record set to the intersection of interest.

Table 2
Distribution of registered ivermectin studies by indication category (n = 253).

Indication category	Studies, n (%)	Completed, n	Unknown status, n	Terminated, withdrawn or suspended, n	Results posted, n (%)
Parasitic or vector-borne	129 (51.0)	96	10	9	30 (23.3)
Viral infection	97 (38.3)	41	40	10	16 (16.5)
Dermatological (non-parasitic)	16 (6.3)	13	1	1	8 (50.0)
Other or pharmacological	8 (3.2)	7	0	1	0 (0)
Oncological	3 (1.2)	0	1	0	0 (0)
<i>Note: rows do not sum to the study total because recruiting, active and not-yet-recruiting statuses are omitted from the table; the complete status breakdown is given in Table S3 and Table S10. Percentages for posted results are calculated within each category.</i>					

Viral indications accounted for slightly more than a third of the corpus. Of the 97 viral-indication records, 93 concerned COVID-19 or SARS-CoV-2 specifically. The remaining four divide evenly. Two are dengue studies from Thailand: NCT02045069, a Phase 2/3 quadruple-masked randomised trial of 360 planned participants, dated March 2016 and still of unknown status; and NCT03432442, a Phase 2 open-label dose-escalation study of pharmacokinetics and pharmacodynamics in 24 paediatric patients, completed in September 2020. The other two treat cutaneous warts (NCT07710638, NCT07396714) and are dated 2027. Neither dengue study has posted results.

The dominance of a single pathogen within the antiviral portfolio is informative. Broad-spectrum antiviral activity has been proposed for ivermectin across several RNA and DNA virus families, yet outside COVID-19 the registered clinical investigation amounts to two dengue trials, both therapeutic in intent and neither reporting results through the registry. This matters for the present proposal in a specific way: the clinical evidence base for a nasal antiviral formulation cannot at present be constructed by analogy to work in other viral indications, because such work has not been registered. It is relevant in this context that failure of ivermectin to reduce dengue viraemia in clinical trials has been noted in the antiviral literature,¹³ so that the sparse non-COVID clinical record is not one of unexplored promise.

A related observation concerns the wider compound class. Thirteen records in the retrieved corpus mention moxidectin, the milbemycin macrocyclic lactone approved by the US Food and Drug Administration in June 2018 for onchocerciasis in people aged 12 years and older. Every one of these records concerns a parasitic indication, and in each moxidectin appears as a comparator or alternative to ivermectin for onchocerciasis, lymphatic filariasis, strongyloidiasis or soil-transmitted helminthiasis. Not one addresses a viral indication. The implications of this for the choice of compound are taken up in the Discussion.

Viral-indication studies: volume, design and temporal concentration

The 97 viral-indication studies had a combined planned enrolment of 65,966 participants, with a median of 150 per study (interquartile range 77 to 400). Eighty-three declared randomised allocation. Masking, however, was declared as absent in 34 studies and as triple or quadruple in only 23. Design attributes are tabulated in full in Table S9.

The corpus is sharply concentrated in time: 84 of the 97 studies carried completion dates in 2020, 2021 or 2022, one carried an earlier date, and twelve carried dates of 2023 or later, six of which extend to 2027 or beyond. Registered antiviral investigation of ivermectin is thus largely a pandemic-era phenomenon, one that has not carried over into the period of Omicron-subvariant circulation. This observation aligns with the concern raised by Wang et al¹⁰ that the prophylaxis evidence base has expanded by essentially one small trial since 2022, and it constrains the inferences that can be drawn about currently circulating variants irrespective of the direction of the earlier results.

Geographic distribution is also uneven (Table S11). Eighty-one of the 97 studies listed sites in a single country, and eleven listed no site at all. Egypt was the most frequently listed location, appearing in 22 records, followed by the United States (11), Thailand and Argentina (7 each). Single-country, single-centre design is no defect in itself, but together with the masking distribution above it limits the weight any individual record can bear.

Prophylaxis constitutes a small minority of the registered work

Fourteen studies satisfied our adjudication criterion for primary prophylaxis of infection (Table 3; full detail in Table S5). This represents 14.4% of viral-indication studies and 5.5% of the whole corpus.

Table 3
Studies adjudicated as primary prophylaxis of infection (n = 14).

Attribute	Value
Study type	12 interventional; 2 observational
Combined planned enrolment	8,573 participants
Median planned enrolment (range)	370 (0 to 4,257)
Registry status	8 completed; 4 unknown; 1 terminated; 1 withdrawn
Masking	6 none; 3 double; 2 triple; 1 quadruple; 2 not stated
Results posted	3 of 14
Nasal or respiratory ivermectin administration	0 of 14

Three features of this set warrant comment. Its size is modest relative to the visibility of the prophylaxis question in public discussion: fewer than one in eighteen registered ivermectin studies addressed

prevention of infection. Methodological quality as declared at registration is uneven, unmasked designs outnumbering triple- or quadruple-masked ones. Most relevant here, not one of the fourteen delivered ivermectin to the nasal or respiratory mucosa.

Two records within this set warrant specific clarification because their titles could be misread as evidence of nasal ivermectin prophylaxis. NCT04701710, a randomised unmasked study of healthcare personnel in Argentina registered with a planned enrolment of 300 and describing a sample of 234 in its registry summary, administered ivermectin orally at 12 mg weekly while delivering iota-carrageenan by nasal spray over four weeks; the nasally applied agent was the carrageenan, not the ivermectin. NCT04425850, a prospective observational cohort of 229 participants, likewise combined an iota-carrageenan nasal spray with ivermectin drops used buccally. A third record, NCT04723459, evaluated ivermectin-impregnated face masks, which is a device, not a mucosal dosage form. None of these three constitutes a test of nasally applied ivermectin; each is listed with its adjudication in Table S13. Additionally, NCT04891250 was withdrawn with zero enrolment and contributes no data.

Local administration is common for dermatological indications and rare for respiratory ones

Forty-five records administered ivermectin by a local route (Table S7). The overwhelming majority were cutaneous: 39 records described topical application in creams, lotions or gels, principally for rosacea, scabies and pediculosis. This body of work is relevant to the present proposal only in a limited sense. It establishes that ivermectin can be formulated as a stable topical semisolid and applied to human skin at 1% with an acceptable tolerability profile, and it removes certain formulation and manufacturing uncertainties. It does not speak to nasal mucosal tolerability, to ciliary function, or to antiviral activity at any site.

Five records administered ivermectin itself to the nasal or respiratory mucosa: four intranasally and one by inhalation (Table 4; full detail in Table S8). Automated route inference would return more than twice that number. The discrepancy matters in itself: a keyword-based reading of the registry substantially overstates how much nasal ivermectin research exists.

Table 4
Studies administering ivermectin by the nasal or respiratory route (n = 5).

Studies administering ivermectin by the nasal or respiratory route (n = 5).					
NCT number	Dosage form	Indication	Design	Country	Registry status
NCT04510233	Nasal formulation, form unspecified	COVID-19	Phase 2; n = 60; unmasked	Not stated	Unknown; no results posted
NCT04681053	Inhaled powder	COVID-19	Phase 3; n = 80; unmasked	Egypt	
NCT04716569	Mucoadhesive nanosuspension, nasal spray	Early COVID-19	Phase 2/3; n = 150; unmasked	Egypt	
NCT04951362	Nanosuspension, nasal spray	Persistent post-COVID anosmia	Phase 2/3; n = 117; unmasked	Egypt	
NCT05269030	Nasal drops	Post-COVID parosmia	Phase 2; n = 60; outcome-assessor masked	Egypt	
Note: n denotes planned enrolment as recorded in the registry; achieved enrolment is not reported for any of these studies. Every study listed had a therapeutic primary purpose.					

The characteristics of this set are uniform and unfavourable. All five studies carry the registry status unknown, meaning that the record has not been updated within the interval defined by the registry; none has posted results; four of the five list sites in a single country and four declare no masking. Their combined planned enrolment is 467 participants, and it cannot be established from the registry whether any of these participants were in fact enrolled. Critically, every one of the five aimed at treatment, not prevention: three addressed established COVID-19 and two addressed post-viral olfactory disturbance, an indication in which the mechanism of interest is not antiviral at all.

No record in the corpus described a semisolid nasal dosage form. The nasal preparations that were registered were sprays, drops and a nanosuspension — that is, precisely the formulation classes most subject to rapid mucociliary clearance.

Cross-registry verification against the WHO ICTRP

The ICTRP search returned 404 unique trial identifiers. Of these, 220 carried ClinicalTrials.gov identifiers, 219 of which were already present in the corpus described above; one further ClinicalTrials.gov record appeared in the ICTRP export but not in the ClinicalTrials.gov export, and 34 records of the ClinicalTrials.gov corpus did not appear in the ICTRP export, discrepancies attributable to differences in indexing and search term between the two exports. The net addition came to 184 records held in registries other than ClinicalTrials.gov, distributed across fourteen national and regional registries, of which the largest contributors were CTRI in India (38), PACTR (28), IRCT in Iran (28), the EU Clinical Trials Register (26) and ISRCTN (23). We provide the full inventory as Table S15.

This is a substantial addition, amounting to 42.1% of the combined corpus of 437 records, and it confirms that reliance on ClinicalTrials.gov alone would materially understate the volume of registered ivermectin research. It does not, however, alter any of the findings reported above. Among the 184 additional records, 89 concerned parasitic or vector-borne indications, 76 concerned viral indications, 14 concerned non-parasitic dermatological indications and five did not name ivermectin in any retrieved field. We adjudicated fourteen studies as primary prophylaxis of infection, listed in Table S16, and every one of them administered ivermectin orally; none used the nasal, inhaled or any other mucosal route, and none used a semisolid dosage form.

No record among the 184 administered ivermectin to the nasal or respiratory mucosa by any route or for any purpose. Five records required route adjudication because the automated inference implied a mucosal or ointment route. In every one the implicated preparation proved to be a different substance: inhaled ciclesonide, an unrelated molnupiravir record, sulfur ointment, a Unani nasal preparation given alongside oral ivermectin tablets, and topical moxidectin compared against topical ivermectin. The failure mode we identified in the ClinicalTrials.gov analysis recurs in the second registry, at a comparable rate.

Taken together, the two sources yield a combined corpus of 437 records containing 173 viral-indication studies and 28 studies adjudicated as primary prophylaxis of infection. Of those 28, none delivered ivermectin to the respiratory mucosa. Across both registries, five studies administered ivermectin nasally or by inhalation, all of them identified in ClinicalTrials.gov, all aimed at treatment, not prevention, and none using a semisolid form. Table S17 sets out the comparison.

Reporting completeness

Summary results had been posted for 16 of 97 viral-indication studies (16.5%), against 30 of 129 (23.3%) for parasitic indications (Table S10). Forty of the 97 viral-indication records (41.2%) carried the status unknown, and a further ten were terminated or withdrawn. The corresponding figure for the nasal and respiratory subset is complete absence: no results, from any of the five studies, at any point since their nominal completion dates of 2020 to 2023.

The same pattern has been noted in systematic review: the Cochrane review identified 28 potentially eligible trials whose results had not been published.⁷

Two cautions apply. Absence of posted summary results does not establish absence of peer-reviewed publication, and we made no attempt to verify the publication status of individual records; these figures measure registry reporting compliance, not the totality of available evidence. Equally, the unknown status designation does not establish that a study was abandoned, only that its record has not been maintained. They do support a narrower claim, and a consequential one. On the specific question of nasally administered ivermectin, the registry yields no retrievable outcome data at all. From these five studies a prospective investigator can learn nothing about whether the approach is tolerable, feasible or futile.

Discussion

What the landscape does and does not support

The cross-tabulation of indication, adjudicated route and purpose (Table S12, and Fig. 3) locates the evidence gap precisely. The cell defined by viral indication, nasal administration and primary prophylactic intent contains no registered study, and the same is true of the inhaled route. This is the intersection at which a preventive nasal ointment would be positioned.

This observation licenses less than it might appear to. It does not constitute evidence that ivermectin prevents viral infection. The trials that have been conducted with adequate power have been null, at doses up to 600 µg/kg daily for six days,⁵ and the pooled prophylaxis estimate reported by Wang et al¹⁰ does not exclude the null despite a favourable point estimate. Nor does it neutralise the concern that in vitro activity may reflect membrane perturbation and assay artefact instead of specific antiviral action. If that reading is right, no route of administration will rescue the compound, and higher local concentrations would raise the risk of non-specific membrane toxicity without delivering a selective antiviral effect. This possibility is a genuine threat to the rationale and should be treated as such, not as a caveat.

What the observation does support is a bounded and testable proposition. The pharmacokinetic explanation for the negative trials — that achievable concentrations at the respiratory epithelium fall below those at which activity is observed in vitro — is the explanation most frequently advanced by proponents and is the one that a change of route directly addresses. If that explanation is correct, the systemic trials have tested a route, not a molecule, and the local route remains unevaluated. If it is incorrect, a local formulation will fail, and it will fail informatively and at modest cost, because the necessary early studies are small. Either outcome resolves a question that has remained open for six years. The value of the proposal lies in its capacity to discriminate between these possibilities, not in any presumption that the favourable one obtains.

Formulation rationale

Three considerations favour a semisolid over the liquid dosage forms that were registered. First, residence time. Mucociliary clearance removes conventional nasal preparations with a half-life of approximately fifteen minutes,¹⁵ which is poorly matched to a prophylactic application whose value depends on maintaining an occupied mucosal surface across an exposure window of hours. Mucoadhesive and semisolid systems address this constraint directly. In rats, a carbopol-containing in situ gel prolonged nasal mucociliary transport time from 10 min for a control solution to 52 min, while preserving mucosal integrity over 14 days of application,⁴³ which illustrates the magnitude of the effect achievable through rheological modification. Second, physicochemical compatibility. Ivermectin is highly lipophilic and poorly water-soluble; aqueous nasal formulation requires nanosuspension or solubilising excipients, whereas a lipophilic ointment base accommodates the molecule without such measures. Third, dose containment. A semisolid applied to the anterior nasal vestibule and turbinate region can be

localised more predictably than a spray, which is relevant both to reproducibility of exposure and to limitation of systemic absorption.

These considerations must be weighed against real disadvantages, which we should state plainly instead of minimising. Semisolid nasal application distributes less uniformly across the nasal mucosa than an atomised spray and may leave posterior regions untreated. Deliberate prolongation of mucosal residence, whether by viscosity or by mucoadhesive polymer, entails interference with a physiological clearance mechanism whose function is defence against inhaled pathogens; agents that reduce ciliary beat frequency raise a safety question that is intrinsic to the mechanism and not incidental to it.^{15,16} Patient acceptability of a nasal ointment applied repeatedly over a prophylactic interval is unestablished. None of these is a decisive objection, but each is an empirical question that must be resolved before efficacy is examined.

Choice of compound within the macrocyclic lactone class

If the rationale for a nasal formulation rests on achieving a local concentration that systemic dosing cannot deliver, the question of which macrocyclic lactone to formulate is not settled by default. Moxidectin is the obvious alternative and deserves an explicit answer instead of being passed over. Figure 4 shows the four candidates in a common orientation, and the differences between them are small enough to make the question a real one. Ivermectin differs from avermectin only by saturation of the C22–C23 bond, and eprinomectin only by an acetylamino group in place of a hydroxyl on the terminal sugar. Moxidectin alone lacks the disaccharide, and carries a methoxime at C23.

Several of its properties appear favourable for a semisolid nasal product. Moxidectin is a milbemycin, not an avermectin, semisynthetically derived from *Streptomyces cyanogriseus*, and was approved by the FDA in 2018 on a modern regulatory dossier, so its human safety characterisation is in some respects more recent than ivermectin's. It is more lipophilic than ivermectin, which is relevant to formulation in a lipophilic ointment base, and it is classified as a Biopharmaceutics Classification System class II compound, of high permeability and low solubility.⁴⁴ Reported partition coefficients differ between sources — log P of 6 for moxidectin against 4.8 for ivermectin in one account, and 5.4 against 4.3 in another — so the absolute values should be treated as approximate, but the direction of the difference is consistent. Phase II and III trials have shown moxidectin to be superior to ivermectin for clearance of *O. volvulus* microfilaridemia with a comparable adverse-event profile,⁴⁴ so the compound is not a speculative one.

Two considerations nonetheless argue against substituting moxidectin, and the first is close to decisive. The experiment that would motivate the substitution has already been performed. Dinesh Kumar et al¹³ compared ivermectin and moxidectin head to head across several in vitro models, precisely because moxidectin is structurally related but metabolically more stable. Both compounds inhibited SARS-CoV-2 in Vero E6 cells; both failed to inhibit it in human airway-derived cell models at concentrations up to 10 µM. The authors concluded that neither a higher-dose regimen of ivermectin nor a switch to another drug in the same class was likely to be useful against SARS-CoV-2 in humans. Whatever weight is given to

that finding, it applies with equal force to both compounds, and moxidectin offers no escape from the central mechanistic objection set out above.

The second consideration is pharmacokinetic, and it inverts the usual argument. Moxidectin's principal advantage in anthelmintic use is its terminal half-life of 20 to 43 days in humans, against approximately one day for ivermectin, together with a large volume of distribution and extensive adipose retention.⁴⁴ For a single-dose oral anthelmintic this is a considerable benefit. For a product applied twice daily to the nasal mucosa across a prophylactic course of several weeks it is a liability. The entire rationale for local administration is to decouple target-site concentration from systemic exposure; a compound that accumulates over a multi-week course with a half-life measured in weeks works against that objective, and any systemic absorption, however small per application, would build up instead of clearing between doses. Ivermectin's short half-life, a disadvantage for systemic anthelmintic dosing, is the appropriate property here.

Two asymmetries favour ivermectin for this application. Ivermectin has established human topical tolerability data at 1% in a cutaneous semisolid, from which the manufacturability and skin-tolerability questions are already partly answered; no topical human formulation of moxidectin exists. And, as the Results record, the registered clinical evidence base for moxidectin contains no viral-indication study at all, so a moxidectin programme would begin from a still narrower base.

One qualification to the second of these points emerged from our cross-registry search, and we record it here. A randomised trial registered in Iran (IRCT20191030045275N1, 100 participants in Egypt) compared a topical formulation of moxidectin, applied once, against topical ivermectin applied daily for three days, for the treatment of human scabies. The moxidectin preparation used was Cydectin, a veterinary pour-on. Human topical application of moxidectin has at least been attempted in a trial, which is more than can be said for the other veterinary members of the class. It is not the same as a human topical product existing. None is licensed, the formulation was developed for percutaneous delivery across bovine skin, and no results have been posted. The argument for ivermectin over moxidectin on grounds of established human topical tolerability is weakened by this record but not overturned.

Abamectin, the parent natural product, is the other candidate that the structural relationship invites, and it can be dealt with more briefly. Abamectin is a mixture of avermectin B1a, at more than 80%, with avermectin B1b, isolated from *Streptomyces avermitilis*; ivermectin is its 22,23-dihydro derivative and differs from it only by saturation of a single double bond. Structurally, abamectin is the closest relative ivermectin has, closer than moxidectin, and if the antiviral activity observed in cell culture belongs to the avermectin scaffold and not to ivermectin specifically, abamectin would be expected to share it. It appears in no record of the retrieved corpus.

The objection to abamectin is not mechanistic but toxicological and regulatory, and it is severe. Abamectin is used principally as an agricultural acaricide and insecticide and in veterinary medicine; documented human exposure is overwhelmingly poisoning, not therapy. In a case series of nineteen human exposures to avermectin insecticides, eighteen of them abamectin, severe outcomes occurred in

six patients at a median ingested dose of 105.5 mg/kg, and one death from multi-organ failure occurred eighteen days after ingestion of 88 mg/kg.⁴⁵ The reported toxidrome progresses from nausea, vomiting and weakness through mydriasis, ptosis, confusion and seizure to coma, respiratory failure, acidosis and, rarely, death. The mechanism underlying this is directly relevant to the route under discussion. Avermectins act on invertebrate glutamate-gated chloride channels but also activate mammalian GABA-A receptors, and the reason human toxicity is low at therapeutic doses is that these compounds do not readily cross the blood–brain barrier.⁴⁵

That last point disqualifies abamectin for a nasal product specifically, and the argument is worth stating because it is not obvious. The safety margin of the avermectin class in humans depends on restricted access to the central nervous system. The nasal mucosa is densely vascular, and the olfactory region provides a route by which substances can reach the brain while partly bypassing the blood–brain barrier – a property actively exploited in nose-to-brain delivery research, and the same property that makes mucoadhesive nasal formulations attractive for centrally acting drugs. Choosing the most CNS-toxic member of the class, and delivering it by the one route designed to circumvent the barrier on which its safety margin depends, would be an unusually poor combination. We offer this as reasoning, not as an empirical finding, since no study of nasal abamectin exposure in humans exists; but the burden of proof would lie heavily on any proposal to proceed.

Two points close the matter. We are aware of no human medicinal product containing abamectin from which a safety dossier, pharmacopoeial specification or pharmaceutical-grade supply could be drawn; the compound is described throughout the veterinary and parasitological literature as an agricultural and veterinary agent, and within the macrocyclic lactone class only ivermectin and moxidectin hold human marketing authorisations, the remainder – abamectin, doramectin, eprinomectin and selamectin – being described in reviews of the class as agents of veterinary use.⁴⁶ A programme would therefore begin without the regulatory foundation that ivermectin's approved status provides. This statement rests on targeted searching of product labelling and the published literature rather than on a systematic survey of national medicines registers, and a human product in a jurisdiction we did not examine cannot be excluded. Nor does abamectin address the mechanistic objection. Dinesh Kumar et al¹³ attributed the dissociation between activity in Vero E6 cells and its absence in human airway epithelium to no feature distinguishing ivermectin from its close analogues, so the parent compound has no reason to behave differently from the dihydro derivative in that model.

Eprinomectin warrants separate consideration, because unlike the others it was designed for topical use and might look like the natural starting point for a topical human product. Chemically it is 4"-epi-acetylamino-4"-deoxy-ivermectin B1, an avermectin comprising predominantly the B1a homologue with a minor B1b component. It was developed for administration across all cattle classes and was the first avermectin with broad activity against both endo- and ectoparasites while leaving minimal residues in meat and milk, and it is described as being highly potent when delivered topically. The marketed pour-on

preparation is approved by the FDA for beef and dairy cattle including lactating animals, at 5 mg/mL, with neither a slaughter withdrawal period nor a milk discard time.⁴⁷

The apparent advantage does not survive examination, for two reasons. The first is regulatory and is stated on the product itself: the label declares that the preparation is not for use in humans and that skin contact should be avoided. There is no human indication, no human pharmacokinetic dataset and no human safety database for eprinomectin in any jurisdiction known to us, so a nasal human product would begin from a position weaker than abamectin's in one respect, since abamectin at least has a documented human toxicology derived from poisoning.

The second reason is more interesting and concerns the property for which eprinomectin was optimised. Its distinguishing feature is minimal partitioning into tissues and milk; that is precisely what permits the zero milk discard time, and it is why the compound was developed. A nasal prophylactic requires the opposite. The object of the formulation described above is to maximise and prolong local concentration at the mucosal surface while minimising systemic exposure, and a molecule selected for low tissue retention is optimised against the first of those aims even as it serves the second. The topical route in which eprinomectin excels is also not the relevant one: percutaneous delivery across bovine skin, from a weatherproof vehicle designed to resist rainfall, bears little relation to retention on a ciliated, continuously cleared human nasal mucosa. We identified no antiviral data for eprinomectin in any human respiratory model.

The same considerations dispose of the remaining veterinary members of the class, doramectin and selamectin, which we found registered only for animal use and for which we identified no human dossier; here too the enquiry was targeted rather than systematic. Table 5 summarises the comparison across the class.

Table 5

Macrocyclic lactones considered as candidate actives for a nasal prophylactic formulation.

Compound	Relation to ivermectin	Human regulatory status	Topical formulation	Bearing on a nasal prophylactic	Records (CTgov + ICTRP)
Ivermectin	—	Approved (onchocerciasis, strongyloidiasis, others)	Human cream 1%	Half-life about 1 day, so no accumulation; human topical tolerability established	253 + 184
Moxidectin	Milbemycin subclass	Approved 2018, onchocerciasis, age ≥ 12	No human product; a veterinary pour-on has been applied topically in one human trial	More lipophilic, but half-life 20–43 days is unsuited to repeated local dosing; inactive in human airway cells	13 + 9
Abamectin	Parent compound	None; agricultural and veterinary	None for humans	Human exposure is poisoning; safety depends on limited CNS access, which the nasal route may bypass	0 + 0
Eprinomectin	Avermectin derivative	None; veterinary, label excludes human use	Bovine pour-on	Optimised for minimal tissue retention, the opposite of a mucosal requirement	0 + 0
Doramectin, selamectin	Avermectin derivatives	None; veterinary	Selamectin spot-on	No human dossier; not considered further	0 + 0

Note: record counts give ClinicalTrials.gov records followed by additional records held only in other registries and retrieved through the WHO ICTRP. No comparative antiviral data for these compounds in a human nasal or airway epithelial model exist, with the single exception of the ivermectin–moxidectin comparison of Dinesh Kumar et al,¹³ in which both compounds were inactive. The table compares developability, not potency. The ICTRP search returned no records for abamectin, eprinomectin, doramectin or selamectin as human interventions; statements in this table that no human medicinal product exists for a given compound rest on targeted searching of product labelling and the published literature rather than on a systematic survey of national medicines registers. The two abamectin records the portal did return concern an unrelated anaesthesia trial and insecticide-treated wall liners for malaria vector control.

The conclusion is not that moxidectin should be excluded permanently. If a nasal ivermectin formulation were to demonstrate activity in a physiologically relevant epithelial model and an adequate local

exposure margin, a comparison against moxidectin in the same system would be a reasonable subsequent step, and moxidectin's greater lipophilicity might prove advantageous for mucosal retention. The argument here is narrower: moxidectin does not rescue the hypothesis if the mechanistic objection is correct, its systemic pharmacokinetics are poorly matched to repeated local dosing, and there is at present no reason to prefer it as the compound with which to test the local-delivery hypothesis. Abamectin, by contrast, should be set aside outright for human nasal use. Across the class, ivermectin is the only compound that combines an approved human indication, an existing topical human formulation, a short half-life appropriate to repeated local dosing, and a documented safety record at scale. Those are the grounds on which it is proposed here. They are grounds of developability, not of demonstrated antiviral superiority, for which no comparative data in a relevant model exist, and that distinction should be preserved in any claim made for the product.

Implications for a development pathway

The registry analysis suggests a sequence in which the questions that can invalidate the approach are addressed first.

Preclinical work should establish, at minimum, that ivermectin at the intended concentration retains antiviral activity in a physiologically relevant model and not in Vero cells alone. The dissociation reported by Dinesh Kumar et al¹³ between activity in Vero E6 cells and absence of activity in human primary bronchial epithelial cells makes reconstituted human nasal epithelium the appropriate test system, and a negative result there would appropriately terminate the programme. Formulation characterisation should quantify residence time, release kinetics and effect on ciliary beat frequency, the last as a safety endpoint in its own right.

The first clinical study should be a tolerability and target-site exposure study in healthy volunteers, with nasal mucosal examination, olfactory assessment and mucociliary clearance measurement as primary endpoints, and quantification of ivermectin in nasal lining fluid alongside plasma concentrations. Tolerability here is not a formality preceding the question of interest; on the evidence reviewed above it is the question most likely to terminate the programme. An efficacious intranasal interferon prophylactic was abandoned because nasal irritation, bleeding and mucosal erosion appeared by the third week of daily administration,³⁴ and a semisolid designed to prolong residence on the mucosa has more reason to be scrutinised on that endpoint, not less. The assessment should run for a period matching the intended prophylactic course, not a few days. The central quantity to be established is whether local concentrations exceed the relevant in vitro inhibitory concentration by a margin sufficient to make an efficacy trial worth conducting, at systemic exposures that remain low. This determination is the pivot of the entire rationale, and until it is made no efficacy claim is supportable.

Only if that condition is satisfied does a prophylaxis trial become justifiable. Its design should avoid the weaknesses evident in the registered prophylaxis set: adequate masking, a defined and verifiable exposure population, laboratory-confirmed infection as the primary endpoint, and a sample size set by a pre-specified effect size, not by convenience. Registration with committed results posting would address

the reporting failure documented in the Results, which has left the existing nasal studies without evidentiary value of any kind.

Limitations

Several limitations constrain the interpretation of our findings. Neither registry indexes all clinical research worldwide, and studies registered in neither source are absent from both; all counts we report are lower bounds. We have, however, addressed the principal limitation of the original design, reliance on a single registry, directly: the ICTRP search added 184 records from fourteen further registries without altering any of the findings, which considerably reduces the likelihood that the central result is an artefact of registry selection. The absolute size of the corpus remains underestimated to an extent that cannot be quantified. Two further cautions attach to the ICTRP step specifically. ICTRP applies bridging to group multiple registrations of one trial, and we did not collapse bridged records, so the figure of 184 should be read as an upper bound on distinct studies. Registry fields also differ substantially in structure and completeness between source registries, and route and dosage form are unstated more often than in ClinicalTrials.gov, so the derived route variable is correspondingly less complete for that subset.

Route, dose and dosage form are not structured registry fields, so we derived them from free text. Dose in mg/kg or µg/kg could be extracted from the Brief Summary for only 10 of 97 viral-indication records, and the route of ivermectin administration was unstated in 146 of 253 records. Studies were not imputed to the oral route in the absence of documentation, which is conservative for the present purpose but means that the oral counts in Table S6 understate actual oral administration; conversely, the “not stated” category should not be read as evidence that a local route was used. We applied the route adjudication described in the Methods only to records for which the automated inference implied a mucosal or ophthalmic route. A record that administered ivermectin nasally without using any recognisable route term anywhere in its title, interventions or summary would not have been detected by either step. We regard this as unlikely, given that a nasal formulation is the salient feature such a record would describe, but it cannot be excluded.

Registration is not conduct. Records with unknown status may correspond to studies that were completed and published, abandoned before enrolment, or never initiated, and the registry does not distinguish these. Similarly, planned enrolment is not achieved enrolment.

A further limitation concerns the comparator landscape described in the Introduction, not the registry analysis itself. We identified the nasally applied antiviral products discussed there through targeted searches, not a systematic survey of national medicines registers, and that account is illustrative, not exhaustive. Additional nasal antiviral semisolids may be registered in this or other jurisdictions, particularly among antiviral ointments of Soviet origin, whose current registration status we did not establish, and the registration status of the interferon preparations differs between jurisdictions and we did not verify it for each. The same qualification applies to the comparison of macrocyclic lactones in the Discussion: the statements there that no human medicinal product exists for abamectin, eprinomectin, doramectin or selamectin rest on targeted searching of product labelling and the published literature, not

on a systematic survey of national medicines registers. Nothing in this limitation bears on the registry findings reported in the Results, which rest on individual examination of all 253 records.

Finally, our adjudication of prophylactic intent, although applied against a stated criterion, involves judgement at the boundary between prevention of infection and prevention of progression.

Conclusions

Our analysis of all 253 ivermectin studies registered on ClinicalTrials.gov, verified against a further 184 records held in fourteen other registries and retrieved through the WHO ICTRP, establishes three findings. Antiviral investigation constitutes 38.3% of the registered corpus but is confined almost entirely to COVID-19 and is concentrated in 2020–2022. Prevention of infection, as distinct from prevention of progression, accounts for 28 studies across both registries, none of which delivered ivermectin to the respiratory mucosa. Nasal and inhaled administration of ivermectin has been registered five times, always for treatment and never for prevention, always without posted results, and never in a semisolid dosage form. Among nasally applied antivirals generally, the semisolid form is occupied regionally by oxolinic ointment, for which no retrievable contemporary controlled evidence exists; the nasal interferon alfa-2b preparations marketed alongside it are liquids, and no contemporary controlled evidence was identified for them in the prophylactic indication either.

Our findings do not support a claim that ivermectin prevents viral infection. The adequately powered oral trials have been null, including at high dose, and the mechanistic basis for antiviral activity has been credibly challenged on grounds that would apply irrespective of route. Any programme proceeding on this basis must treat the possibility that the compound has no specific antiviral activity as a live hypothesis, not a formality.

What our findings do establish is that the hypothesis most frequently offered to explain the negative trials — insufficient drug concentration at the respiratory epithelium — has never been tested by the intervention that would test it. A nasally applied semisolid is a legitimate object of early-phase investigation, provided it is pursued in the order the evidence requires: activity in a physiologically relevant epithelial model, then mucosal tolerability and target-site exposure in healthy volunteers, and only then — if the exposure margin proves adequate — a properly powered and masked prophylaxis trial. Framed in this way, the proposal is falsifiable at each stage and at modest cost. Framed as a promising preventive agent in advance of such data, it would repeat two errors at once: the one that produced the registered corpus described here, and the older one represented by the nasal antiviral semisolids already on sale in this region for prophylaxis of influenza and acute respiratory infection, on evidence that can no longer be examined. The intranasal interferon experience supplies the further caution that mucosal tolerability over a prolonged course, rather than efficacy, may prove the binding constraint.

Abbreviations

AMA

American Medical Association
ARI
acute respiratory infection
BCS
Biopharmaceutics Classification System
CI
confidence interval
CNS
central nervous system
COVID-19
coronavirus disease 2019
FDA
US Food and Drug Administration
GABA
gamma-aminobutyric acid
ICTRP
International Clinical Trials Registry Platform
IQR
interquartile range
NCT
National Clinical Trial (ClinicalTrials.gov identifier)
OTC
over the counter
PCR
polymerase chain reaction
RCT
randomised controlled trial
RSV
respiratory syncytial virus
SARS-CoV-2
severe acute respiratory syndrome coronavirus 2
SmPC
Summary of Product Characteristics
WHO
World Health Organization.

Declarations

Supplementary Material

Supplementary Tables S1 to S17 are provided as a single Microsoft Excel workbook. Table S1 documents data provenance and derived-variable definitions; Table S2 contains the complete extracted ClinicalTrials.gov dataset; Tables S3 to S12 contain the analyses summarised in the Results; Table S13 lists the record-level route adjudications with the reason for each. Tables S14 to S17 cover the WHO ICTRP cross-registry verification: provenance and procedure, the inventory of 184 records held only in other registries, the prophylaxis studies among them, and a comparison of the two sources.

Data Sharing Statement

All data analysed in this study are publicly available records from ClinicalTrials.gov, maintained by the US National Library of Medicine.⁴¹ The complete extracted dataset, comprising all 253 records with every retrieved field and every derived variable, is provided as Supplementary Table S2, and the full derivation and adjudication rules are documented in Supplementary Tables S1 and S13, so that all reported analyses can be reproduced or revised independently. No additional unpublished data were generated. The date of the registry export is stated in the Methods; because registry contents change continuously, all counts are specific to that snapshot.

Ethics Approval and Informed Consent

This study analysed publicly accessible, aggregate registry records of clinical studies. It involved no human participants, no identifiable individual data, no human tissue and no animals. Institutional review board approval and informed consent were therefore not required, and none was sought.

Consent for Publication

Not applicable. This article contains no images, videos, recordings or case details relating to any identifiable individual.

Disclosure

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Author Contributions

All authors made a contribution to the work reported, whether in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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References

1. Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM (2020) The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. *Antiviral Res* 178:104787. 10.1016/j.antiviral.2020.104787
2. Schmith VD, Zhou JJ, Lohmer LRL (2020) The approved dose of ivermectin alone is not the ideal dose for the treatment of COVID-19. *Clin Pharmacol Ther* 108(4):762–765. 10.1002/cpt.1889
3. Reis G, Silva EASM, Silva DCM et al (2022) TOGETHER Investigators. Effect of early treatment with ivermectin among patients with Covid-19. *N Engl J Med* 386(18):1721–1731. 10.1056/NEJMoa2115869
4. Naggie S, Boulware DR, Lindsell CJ et al (2022) Effect of ivermectin vs placebo on time to sustained recovery in outpatients with mild to moderate COVID-19: a randomized clinical trial. *JAMA* 328(16):1595–1603. 10.1001/jama.2022.18590
5. Naggie S, Boulware DR, Lindsell CJ et al (2023) Effect of higher-dose ivermectin for 6 days vs placebo on time to sustained recovery in outpatients with COVID-19: a randomized clinical trial. *JAMA* 329(11):888–897. 10.1001/jama.2023.1650
6. Hayward G, Yu LM, Little P et al (2024) Ivermectin for COVID-19 in adults in the community (PRINCIPLE): an open, randomised, controlled, adaptive platform trial of short- and longer-term outcomes. *J Infect* 88(4):106130. 10.1016/j.jinf.2024.106130
7. Popp M, Reis S, Schießer S et al (2022) Ivermectin for preventing and treating COVID-19. *Cochrane Database Syst Rev* 6(6):CD015017. 10.1002/14651858.CD015017.pub3
8. Satyam SM, El-Tanani M, Patni MA et al (2025) Repurposing anthelmintic drugs for COVID-19 treatment: a meta-analysis of randomized clinical trials on ivermectin and mebendazole. *Antibiot (Basel)* 14(5):459. 10.3390/antibiotics14050459
9. Sai Yengu N, Raheem A, Pons AG et al (2025) The impact of ivermectin on COVID-19 outcomes: a systematic review and meta-analysis. *Ann Med Surg (Lond)* 87(2):809–829.

10.1097/MS9.0000000000002762

10. Wang X, Meng J, Li Y et al (2026) The role of ivermectin in the prevention and treatment of SARS-CoV-2 infection: a meta-analysis of randomized controlled trials. *BMC Infect Dis* 26(1):1035. 10.1186/s12879-026-13195-9
11. Wagstaff KM, Stein MS, Herschtal A et al (2025) A pilot, randomised, placebo-controlled, double-blind trial of a single oral dose of ivermectin for post-exposure prophylaxis of SARS-CoV-2. *Pharmaceutics* 17(9):1205. 10.3390/pharmaceutics17091205
12. Eastman RT, Rusinova R, Herold KF et al (2025) Membrane perturbations and assay interferences by ivermectin explain its in vitro SARS-CoV-2 antiviral activities and lack of translatability. *J Med Chem* 68(20):20979–21002. 10.1021/acs.jmedchem.5c01610
13. Dinesh Kumar N, Ter Ellen BM, Bouma EM et al (2022) Moxidectin and ivermectin inhibit SARS-CoV-2 replication in Vero E6 cells but not in human primary bronchial epithelial cells. *Antimicrob Agents Chemother* 66(1):e0154321. 10.1128/AAC.01543-21
14. Sungnak W, Huang N, Bécavin C et al (2020) HCA Lung Biological Network. SARS-CoV-2 entry factors are highly expressed in nasal epithelial cells together with innate immune genes. *Nat Med* 26(5):681–687. 10.1038/s41591-020-0868-6
15. Pathak K (2011) Mucoadhesion: a prerequisite or a constraint in nasal drug delivery? *Int J Pharm Investig* 1(2):62–63. 10.4103/2230-973X.82383
16. Ugwoke MI, Verbeke N, Kinget R (2001) The biopharmaceutical aspects of nasal mucoadhesive drug delivery. *J Pharm Pharmacol* 53(1):3–22. 10.1211/0022357011775145
17. Eccles R, Meier C, Jawad M, Weinmüllner R, Grassauer A, Prieschl-Grassauer E (2010) Efficacy and safety of an antiviral iota-carrageenan nasal spray: a randomized, double-blind, placebo-controlled exploratory study in volunteers with early symptoms of the common cold. *Respir Res* 11(1):108. 10.1186/1465-9921-11-108
18. Ludwig M, Enzenhofer E, Schneider S et al (2013) Efficacy of a carrageenan nasal spray in patients with common cold: a randomized controlled trial. *Respir Res* 14(1):124. 10.1186/1465-9921-14-124
19. Eccles R, Winther B, Johnston SL, Robinson P, Trampisch M, Koelsch S (2015) Efficacy and safety of iota-carrageenan nasal spray versus placebo in early treatment of the common cold in adults: the ICICC trial. *Respir Res* 16(1):121. 10.1186/s12931-015-0281-8
20. Figueroa JM, Lombardo ME, Dogliotti A et al (2021) Efficacy of a nasal spray containing iota-carrageenan in the postexposure prophylaxis of COVID-19 in hospital personnel dedicated to patients care with COVID-19 disease. *Int J Gen Med* 14:6277–6286. 10.2147/IJGM.S328486
21. Klusmann JP, Grosheva M, Meiser P et al (2023) Early intervention with azelastine nasal spray may reduce viral load in SARS-CoV-2 infected patients. *Sci Rep* 13(1):6839. 10.1038/s41598-023-32546-z
22. Lehr T, Meiser P, Selzer D et al (2025) Azelastine nasal spray for prevention of SARS-CoV-2 infections: a phase 2 randomized clinical trial. *JAMA Intern Med* 185(11):1309–1317. 10.1001/jamainternmed.2025.4283

23. Tandon M, Wu W, Moore K et al (2022) SARS-CoV-2 accelerated clearance using a novel nitric oxide nasal spray (NONS) treatment: a randomized trial. *Lancet Reg Health Southeast Asia* 3:100036. 10.1016/j.lansea.2022.100036
24. Castellarnau A, Heery GP, Seta A et al (2022) Astodimer sodium antiviral nasal spray for reducing respiratory infections is safe and well tolerated in a randomized controlled trial. *Sci Rep* 12(1):10210. 10.1038/s41598-022-14601-3
25. Mupirocin calcium nasal ointment 2% Prescribing information. Available from: <https://www.medicines.org.uk/emc/product/100916/pil#gref>
26. Özkan B, Altuntaş E, Ünlü Ü, Doğan HH, Özsoy Y, Çakır Koç R (2023) Development of an antiviral ion-activated in situ gel containing 18 β -glycyrrhetic acid: an alternative against respiratory syncytial virus. *Pharmaceutics* 15(8):2055. 10.3390/pharmaceutics15082055
27. Ministry of Health of Ukraine Oxolinic ointment, nasal, 2.5 mg/g (TOV Ternofarm), marketing authorisation UA/14265/01/01: summary of product characteristics [in Ukrainian]. State Register of Medicinal Products of Ukraine. Available from: <https://www.drlz.com.ua>. Accessed 14 September 2026
28. JSC Farmak NAZOFERON® (interferon alfa-2b): instructions for medical use [in Ukrainian]. Nasal drops, 100,000 IU/mL, registration certificate UA/15653/02/01; nasal spray, not less than 100,000 IU/mL, registration certificate UA/20260/01/01 (Ministry of Health of Ukraine Order No. 1979 of 17 November 2023). State Register of Medicinal Products of Ukraine. Available from: <https://farmak.ua/drugs/nazoferon-spray/>
29. Bezdieniezhykh N, Lykhova O, Borshchevskiy G, Kruglov Ye, Borshchevska M (2025) Evaluation of the duration of new nasal drug interferon α -2b activity in an experimental model system. *Virol J* 22(1):96. 10.1186/s12985-025-02678-x
30. Mikheyev A, Propistsova E, Huang S (2020) A forgotten Soviet drug: meta-analysis supports the efficacy of oxoline, a broadly antiviral compound, for influenza prophylaxis [Preprint]. SSRN. 10.2139/ssrn.3562462
31. Zhao Y, Gao Y, Guyatt G et al (2024) Antivirals for post-exposure prophylaxis of influenza: a systematic review and network meta-analysis. *Lancet* 404(10454):764–772. 10.1016/S0140-6736(24)01357-6
32. Douglas RM, Moore BW, Miles HB et al (1986) Prophylactic efficacy of intranasal alpha2-interferon against rhinovirus infections in the family setting. *N Engl J Med* 314(2):65–70. 10.1056/NEJM198601093140201
33. Hayden FG, Albrecht JK, Kaiser DL, Gwaltney JM Jr (1986) Prevention of natural colds by contact prophylaxis with intranasal alpha2-interferon. *N Engl J Med* 314(2):71–75. 10.1056/NEJM198601093140202
34. Farr BM, Gwaltney JM Jr, Adams KF, Hayden FG (1984) Intranasal interferon-alpha 2 for prevention of natural rhinovirus colds. *Antimicrob Agents Chemother* 26(1):31–34. 10.1128/AAC.26.1.31

35. Zadorozhna VI, Serheieva TA, Shahinian VR, Vynnyk NP, Demchyshyna IV, Murashko OV (2024) Epidemiological characteristics of acute respiratory infections and influenza in the season 2023–2024 [in Ukrainian]. *Prev Med* 410.61948/prevmed-2024-4-30
36. Newitt S, Mironenko A, Holubka O et al (2018) Rapid risk assessment during the early weeks of the 2015–2016 influenza season in Ukraine. *Influenza Other Respir Viruses* 12(2):241–249. 10.1111/irv.12526
37. Center for Public Health of the Ministry of Health of Ukraine Incidence of influenza and acute respiratory viral infections in Ukraine [in Ukrainian]. Available from: <https://phc.org.ua/kontrol-zakhvoryuvan/inshi-infekciyni-zakhvoryuvannya/zakhvoryuvanist-na-grip-ta-grvi-v-ukraini>
38. Ministry of Health of Ukraine Calendar of prophylactic vaccinations in Ukraine, approved by Order No. 595 of 16 September 2011, as subsequently amended [in Ukrainian]. Available from: <https://zakon.rada.gov.ua/laws/show/z1159-11>
39. Public Health Center of the Ministry of Health of Ukraine. The 2025–2026 epidemic season of acute respiratory viral infection has begun in Ukraine [in Ukrainian]. 30 (2025) September Available from: <https://phc.org.ua/news/v-ukraini-startuvav-epidsezon-grvi-2025-2026-rr>
40. Public Health Center of the Ministry of Health of Ukraine. The 2025–2026 epidemic season of acute respiratory viral infection has ended in Ukraine [in Ukrainian]. 27 (2026) May Available from: <https://phc.org.ua/news/v-ukraini-zavershivsya-epidsezon-grvi-2025-2026-rokiv>
41. US National Library of Medicine ClinicalTrials.gov [dataset]. Available from: <https://clinicaltrials.gov>
42. World Health Organization International Clinical Trials Registry Platform (ICTRP) Search Portal [dataset]. Available from: <https://trialsearch.who.int>
43. Zaki NM, Awad GA, Mortada ND, Abd Elhady SS (2007) Enhanced bioavailability of metoclopramide HCl by intranasal administration of a mucoadhesive in situ gel with modulated rheological and mucociliary transport properties. *Eur J Pharm Sci* 32(4–5):296–307. 10.1016/j.ejps.2007.08.006
44. Milton P, Hamley JID, Walker M, Basáñez MG (2020) Moxidectin: an oral treatment for human onchocerciasis. *Expert Rev Anti Infect Ther* 18(11):1067–1081. 10.1080/14787210.2020.1792772
45. Pirasath S, Nageswaran B, Karunasena RPV, Gevakaran M (2021) Acute abamectin toxicity: a case report. *Toxicol Commun* 5(1):66–68. 10.1080/24734306.2021.1881233
46. Prichard RK, Geary TG (2019) Perspectives on the utility of moxidectin for the control of parasitic nematodes in the face of developing anthelmintic resistance. *Int J Parasitol Drugs Drug Resist* 10:69–83. 10.1016/j.ijpddr.2019.06.002
47. Boehringer Ingelheim Animal Health USA EPRINEX (eprinomectin) Pour-On for beef and dairy cattle. Product label, NADA 141 – 079. DailyMed, US National Library of Medicine. Available from: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=7cf8669c-c000-4645-962e-891946c0e54b&audience=consumer>

Figures

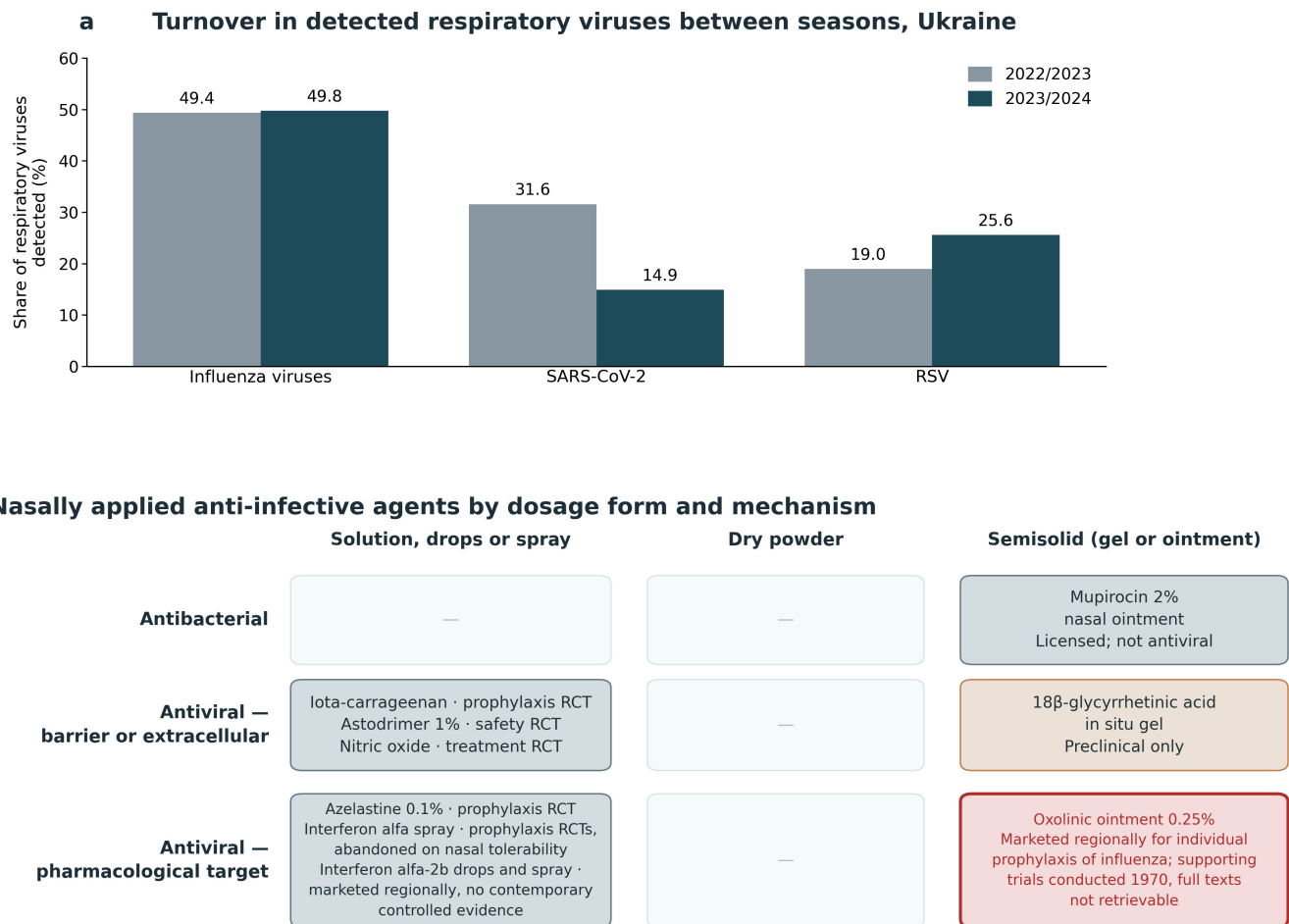


Figure 1

Turnover in detected respiratory viruses in Ukraine, and the landscape of nasally applied anti-infective agents by dosage form and mechanism, showing that the semisolid antiviral form is occupied only by a product whose supporting evidence cannot be appraised. **(a)** Share of respiratory viruses detected under sentinel surveillance in Ukraine, comparing the 2022/2023 and 2023/2024 seasons. The three categories shown are not exhaustive and do not sum to 100%: adenoviruses, parainfluenza viruses and rhinoviruses accounted for the remainder and increased between these seasons. Values are taken from Zadorozhna et al,³⁵ as cited beneath Table 1. **(b)** Nasally applied anti-infective agents in clinical use or clinical testing, arranged by dosage form and by mechanism of action. Interferon alfa appears twice in the solution, drops or spray cell: as the high-dose spray whose prophylactic efficacy against rhinovirus was demonstrated in randomised trials in the 1980s and whose development was halted on nasal tolerability rather than efficacy, and as the recombinant alfa-2b drops and metered spray marketed regionally today, which are liquid preparations and not semisolids. Descriptors give the highest stage of evidence reached by each agent rather than a judgement of its efficacy; the prophylaxis trials indicated rest on small numbers of events and are described in the Introduction. The outlined cell is the position a nasally applied ivermectin ointment would occupy, and it is already occupied. Oxolinic ointment 0.25% is marketed regionally for individual prophylaxis of influenza, and recombinant interferon alfa-2b is

marketed for prophylaxis of acute respiratory viral infection as nasal drops and as a metered spray, both of which are liquid preparations; the trials supporting oxolin were conducted in 1970 and their full texts are not retrievable, and no contemporary controlled evidence was identified for the nasal interferon preparations in the prophylactic indication. The gap identified here is therefore not an empty dosage form but an absence of appraisable evidence within it. The products shown were identified by targeted rather than systematic search and are illustrative rather than exhaustive.

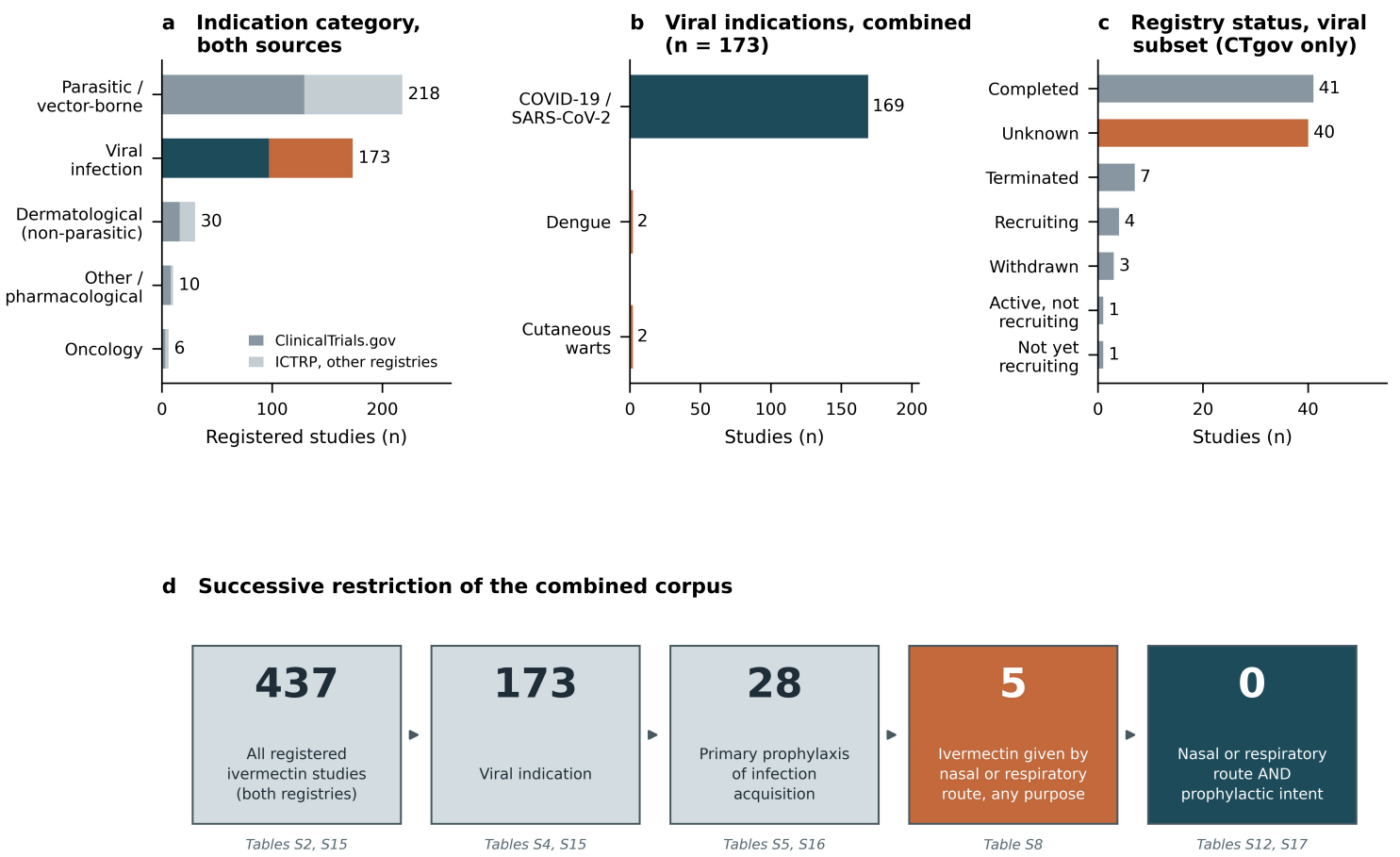


Figure 2

Composition of the registered ivermectin evidence base across both registry sources, and successive narrowing to the intersection of interest. (a) Distribution of studies across indication categories, with each bar partitioned into records retrieved from ClinicalTrials.gov and additional records held only in other registries and retrieved through the WHO ICTRP; the viral-indication row is shown in the accent colours. (b) Composition of the 173 viral-indication records of the combined corpus by pathogen. Every one of the 76 additional ICTRP records concerned COVID-19, so the two dengue and two cutaneous wart studies derive from ClinicalTrials.gov alone. (c) Registry status of the 97 viral-indication records held in ClinicalTrials.gov. This panel is restricted to that source because the status vocabulary used by ICTRP partner registries is coarser and not comparable. (d) Successive restriction of the combined corpus of

437 records to viral indications, to studies adjudicated as primary prophylaxis of infection acquisition, to studies administering ivermectin itself to the nasal or respiratory mucosa, to the intersection of nasal or respiratory administration and prophylactic intent, which is empty in both registries. Counts in panel d are not nested in a single sequence: the last two categories are disjoint subsets of the viral-indication records rather than successive restrictions of one another, and their intersection is shown as zero. All five studies administering ivermectin nasally or by inhalation were identified in ClinicalTrials.gov; the ICTRP search added none. Route throughout is the adjudicated route of ivermectin administration, defined in the Methods and listed record by record in Tables S13 and S15. Values are derived from the two registry exports analysed in this study and are reproduced in Supplementary Tables S3, S5, S8, S12 and S15 to S17.

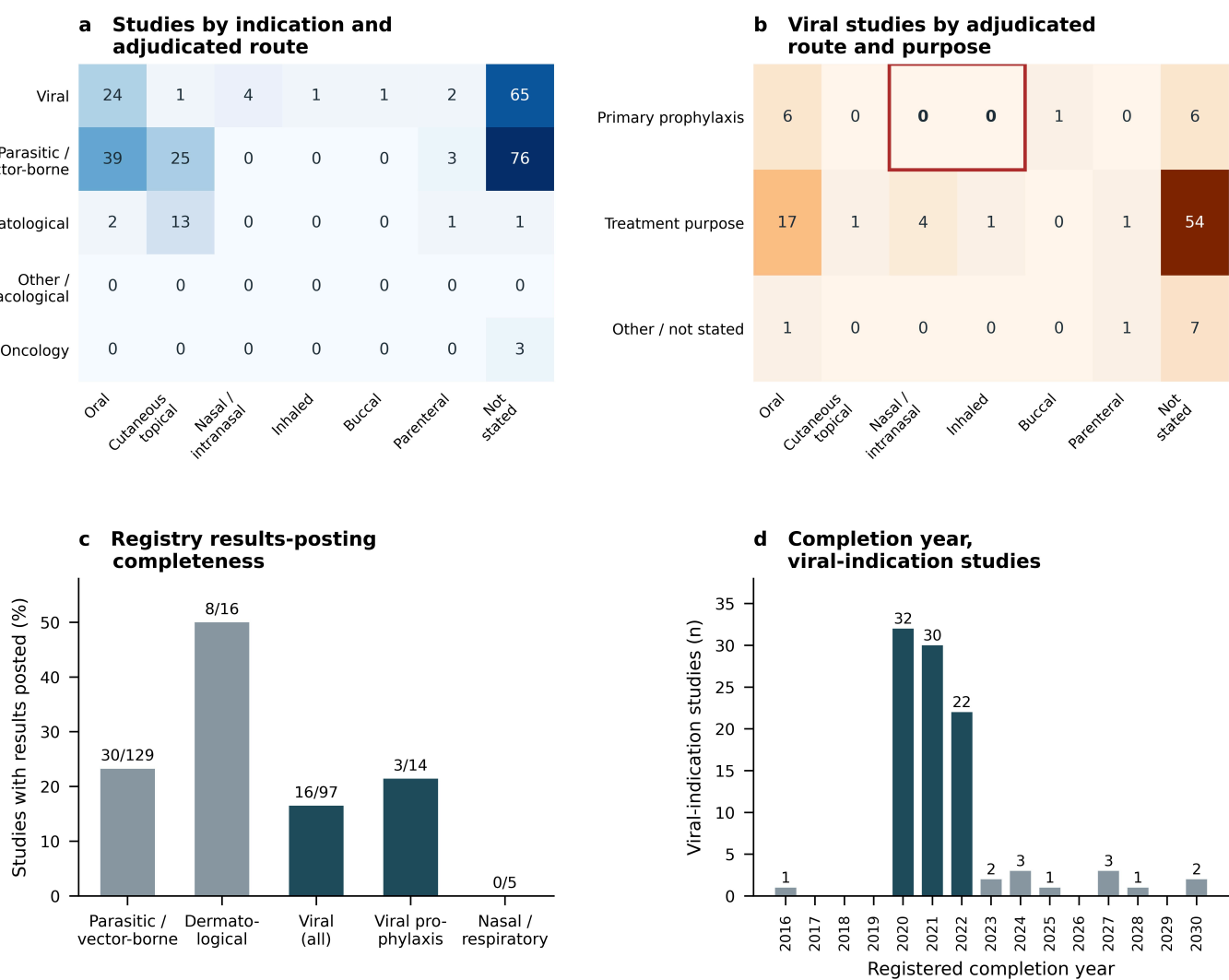
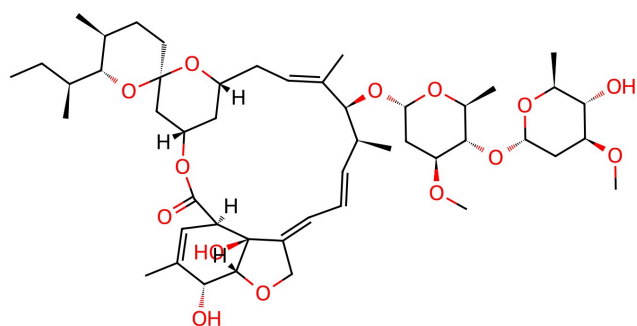


Figure 3

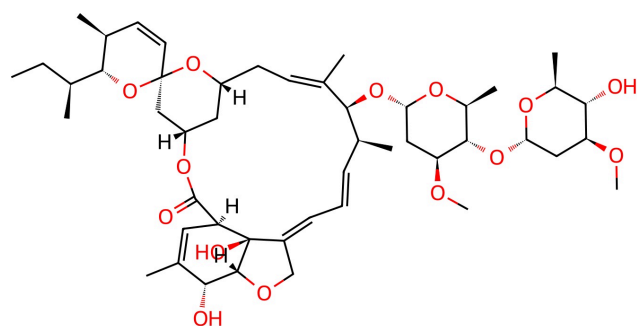
Administration route, study purpose and reporting completeness across the registered corpus. **(a)** Number of registered studies by indication category and adjudicated route of ivermectin administration. Routes are not mutually exclusive and were not imputed where the registry fields did not state them, so

the “not stated” column reflects documentation rather than absence of a route. **(b)** Within viral-indication studies, the number of studies by adjudicated route and by study purpose. The outlined cells are the nasal and inhaled routes under primary prophylactic intent, both of which are empty; primary prophylaxis was pursued only through oral or buccal administration, or with the route unstated. **(c)** Proportion of studies with summary results posted to ClinicalTrials.gov, by indication category, with the nasal or respiratory subset shown separately; the denominator for each bar is given above it. **(d)** Completion year of viral-indication studies, showing the concentration of the corpus in 2020 to 2022. Values are derived from the registry export analysed in this study and are reproduced in Supplementary Tables S6, S8, S10, S12 and S13.

a**C48H74O14** MW 875.11 g/mol

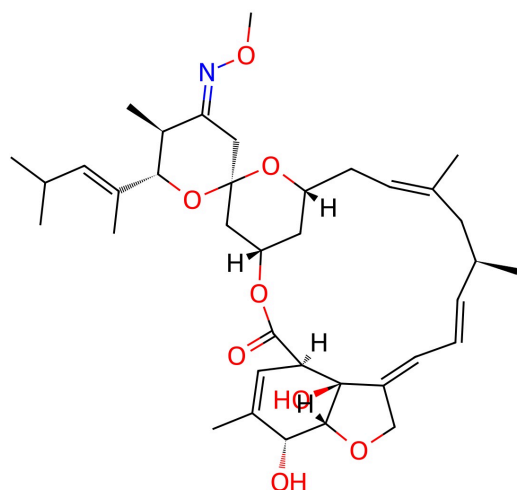
Approved for human use; the compound proposed here

InChIKey AZSNMRSAGSSBNP-XPNUAGNSA-N

Ivermectin B1a 22,23-dihydroavermectin B1a**b****C48H72O14** MW 873.09 g/mol

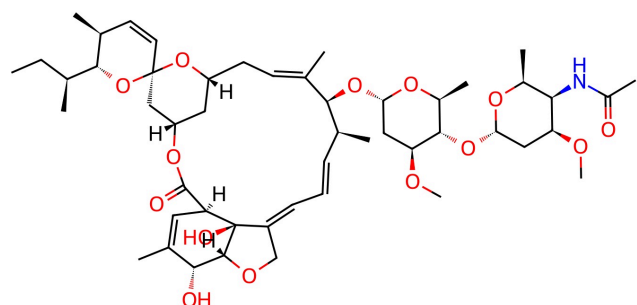
Parent compound; no human medicinal product

InChIKey RRZXIRBKLT SOM-XPNUAGNSA-N

Avermectin B1a major component of abamectin**c****C37H53NO8** MW 639.83 g/mol

Approved 2018 for onchocerciasis; half-life 20-43 d

InChIKey YZBLFMPOMVTDJY-LSGXYNIPSA-N

Moxidectin milbemycin subclass**d****C50H75NO14** MW 914.14 g/mol

Veterinary only; optimised for low tissue residues

InChIKey ZKWQXZUCOBISE-CRTGXIDZSA-N

Eprinomectin B1a 4'-epi-acetylamino-4''-deoxyavermectin B1a**Figure 4**

Structures of the macrocyclic lactones considered as candidate actives for a nasal prophylactic formulation, drawn in a common orientation to permit direct comparison. **(a)** Ivermectin B1a, the 22,23-dihydro derivative of avermectin B1a and the compound proposed here. **(b)** Avermectin B1a, the major component of abamectin, differing from (a) only by the C22–C23 double bond. **(c)** Moxidectin, a milbemycin, which lacks the oleandrose disaccharide at C13 and carries a methoxime substituent. **(d)**

Eprinomectin B1a, differing from (a) by an acetylamino group in place of the 4"-hydroxyl of the terminal sugar and by the C22–C23 double bond. Ivermectin, abamectin and eprinomectin are marketed as mixtures of a major B1a and a minor B1b homologue differing in the C25 substituent (sec-butyl in B1a, isopropyl in B1b); the B1a component is shown in each case.

Supplementary Files

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