



BMJ Open Understanding the widespread use of veterinary ivermectin for Chagas disease, underlying factors and implications for the COVID-19 pandemic: a convergent mixed-methods study

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ABSTRACT

Objectives Veterinary ivermectin (vet-IVM) has been used widely in Latin America against COVID-19, despite the lack of scientific evidence and potential risks. Widespread vet-IVM intake was also discovered against Chagas disease during a study in Bolivia prior to the pandemic. All vet-IVM-related data were extracted to understand this phenomenon, its extent and underlying factors and to discuss potential implications for the current pandemic.

Design A convergent mixed-methods study design including a survey, qualitative in-depth interviews (IDI) and focus group discussions (FGD).

Setting A cross-sectional study conducted in 2018 covering the geographic area of Monteagudo, an endemic municipality for Chagas disease.

Participants A total of 669 adult household representatives from 26 communities participated in the survey, supplemented by 14 IDI and 2 FGD among patients, relatives and key informants.

Results 9 IDI and 2 FGD contained narratives on vet-IVM use against Chagas disease. Five main themes emerged: (1) the extent of the vet-IVM phenomenon, (2) the perception of vet-IVM as a treatment for Chagas disease, (3) the vet-IVM market and the controversial role of stakeholders, (4) concerns about potential adverse events and (5) underlying factors of vet-IVM use against Chagas disease.

In quantitative analysis, 28% of participants seropositive for Chagas disease had taken vet-IVM. Factors associated with multivariate analysis were advanced age (OR 17.01, 95 CI 1.24 to 36.55, $p=0.027$ for age above 60 years), the experience of someone close as information source (OR 3.13, 95 CI 1.62 to 5.02, $p<0.001$), seropositivity for Chagas disease (OR 3.89, 95 CI 1.39 to 6.20, $p=0.005$) and citing the unavailability of benznidazole as perceived healthcare barrier (OR 2.3, 95 CI 1.45 to 5.18, $p=0.002$). Participants with an academic education were less likely

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ The use of a mixed-methods design, representative geographic coverage and the inclusion of a wide range of relevant stakeholders enabled a holistic understanding of the local situation.
- ⇒ Several data sources were triangulated to understand the extent of veterinary ivermectin (vet-IVM) use and its importance in the context of different treatment schemes against Chagas disease.
- ⇒ Not bringing up vet-IVM on purpose complicated the assessment of data saturation during qualitative interviews, since participants not talking about vet-IVM spontaneously might have had a different opinion or attribute less importance to the topic.
- ⇒ The study was conducted in one Bolivian municipality prior to the COVID-19 pandemic and cannot be generalised to other regions, nor to the current situation, but only carefully discuss potential implications.

to report vet-IVM intake (OR 0.12, 95 CI 0.01 to 0.78, $p=0.029$).

Conclusions Social determinants of health, the unavailability of treatment and a wonder drug image might contribute to the phenomenon of vet-IVM.

INTRODUCTION

Ivermectin is a broad-spectrum antiparasitic agent that was discovered in the 1970s and played a fundamental role in control programmes targeting neglected tropical diseases (NTDs) such as onchocerciasis and lymphatic filariasis. Originally approved as a veterinary drug, ivermectin drug donation programmes helped to reduce chronic

morbidity and disability as well as the social consequences of severely stigmatised diseases for vulnerable human populations.¹ Ivermectin's discoverers were honoured with the Nobel Prize in 2015.²

Ivermectin belongs to the family of avermectins. It binds to glutamate-gated chloride ion channels, which are present in invertebrate nerve and muscle cells, and causes paralysis and death of the parasite. Its characteristics to treat several helminths, as well as ectoparasites, made it an endo-ecto antiparasitic, which is easily available and effective at treating a broad range of parasites in livestock. It has an excellent safety profile when administered at standard doses. Ivermectin has been used for decades in large-scale drug administration programmes.³

Ivermectin and COVID-19

In 2020, Caly *et al* described potential efficacy of ivermectin against SARS-CoV-2 in vitro, although in much higher doses than approved for human usage.⁴ Since then, several trials of ivermectin efficacy against COVID-19 have been conducted, both for prevention and treatment of the infection, although most of the completed studies are small and few are considered high quality.⁵⁻⁷ Current scientific evidence suggests that ivermectin does not have a positive impact on COVID-19-related clinical end points. The unfavourable pharmacokinetics of ivermectin in COVID-19 moreover lead to difficulties in maintaining adequate serum concentration.⁸ A Cochrane systematic review concluded that the reliable evidence available does not support the use of ivermectin either to treat or to prevent COVID-19.⁹

Ivermectin and Chagas disease

Chagas disease (CD) is caused by a parasite called *Trypanosoma cruzi*, which is mainly transmitted by triatomine vectors. After an indeterminate phase that can last for decades, patients with CD may develop chronic cardiac or gastrointestinal complications.¹⁰ CD is considered an NTD that can lead to mental distress, stigmatisation and participation restriction.¹¹ Several authors have moreover highlighted negative COVID-19 implications on NTD-affected population, such as COVID-19's potential impact on the heart of the over 1 million people with chronic Chagas cardiomyopathy worldwide.^{12 13} Since treatment with benznidazole (BNZ) seems not to be effective in advanced disease,¹⁴ early diagnosis and treatment is an important strategy to prevent chronic morbidity. BNZ access however continues to be restricted.¹⁵ Apart from BNZ, a wide range of complementary medicines has been described to be used to halt the progression of CD, including (veterinary) ivermectin (vet-IVM).¹⁶

Based on ivermectin's insecticide properties, a potential use against vectors transmitting infectious diseases, such as mosquitoes, ticks or bugs has been suggested. Dias *et al* showed that CD-transmitting vectors died if feeding on dogs after their intake of ivermectin.¹⁷ Although this effect only lasted 2 days after administration of the drug, the authors postulated that there may be potential in

using ivermectin in vector control activities. To our knowledge, a connection between ivermectin and *T. cruzi* has never been described in the literature (in neither animal reservoirs nor humans).^{1 17} To the best of our knowledge, there is currently no evidence that would justify CD treatment with ivermectin.

Misuse of ivermectin against COVID-19 and Chagas disease

Since Caly *et al* described the effectiveness of ivermectin against COVID-19 in vitro,⁴ there has been a surge in demand in Latin-American countries. Some countries such as Bolivia and Peru included ivermectin in national plans to fight COVID-19, and Bolivia even distributed 350 000 doses in the city of Trinidad.¹⁸ Apart from this, widespread auto-medication with vet-IVM has been reported.¹⁹ In Peru, the injection of vet-IVM in 5000 individuals from indigenous communities by Evangelical groups, calling it a 'salvation', made news headlines.²⁰ Several of these individuals reported adverse side effects, such as tachycardia. The increased demand for ivermectin caused the Food and Drug Administration to put out a warning over its use, and an ongoing scientific debate about the need for rigorousness, clinical trials and the handling of premature scientific information in light of the COVID-19 pandemic.²¹ While the global scientific community underwent an unprecedented efforts race to identify effective drugs to address the pandemic,²² the large-scale use of drugs such as ivermectin poses an imminent environmental risk^{23 24} and is linked to the loss of biodiversity, an important cause of the current pandemic.

The unscientific use of vet-IVM for unapproved diseases seems, however, not to be a new phenomenon. In a representative mixed-methods study on knowledge, perceptions and treatment practices carried out in Monteagudo (Bolivia) in the pre-COVID-19 era in 2018, widespread intake of vet-IVM against CD emerged to an extent that had never been described before.²⁵ In light of the current ivermectin hype and use of vet-IVM for COVID-19 in Bolivia and its neighbouring countries, we conducted an in-depth analysis on all vet-IVM-related narratives and survey data. The aim of this analysis was to better understand this phenomenon, its extent and the potential underlying factors.

METHODS

Study setting

The municipality of Monteagudo lies in the middle of the Bolivian Chaco, a region known for its high CD prevalence. Although CD-related morbidity is not monitored within official health statistics, a high burden caused by chronic CD complications has been described.²⁶ The 97 communities of Monteagudo are widely dispersed, with long walking distances between individual households in remote settings. Apart from 17 local health centres, there are 2 hospitals in the town of Monteagudo.

Study design

A mixed-methods study was conducted from September to December 2018 in the Municipality of Monteagudo,

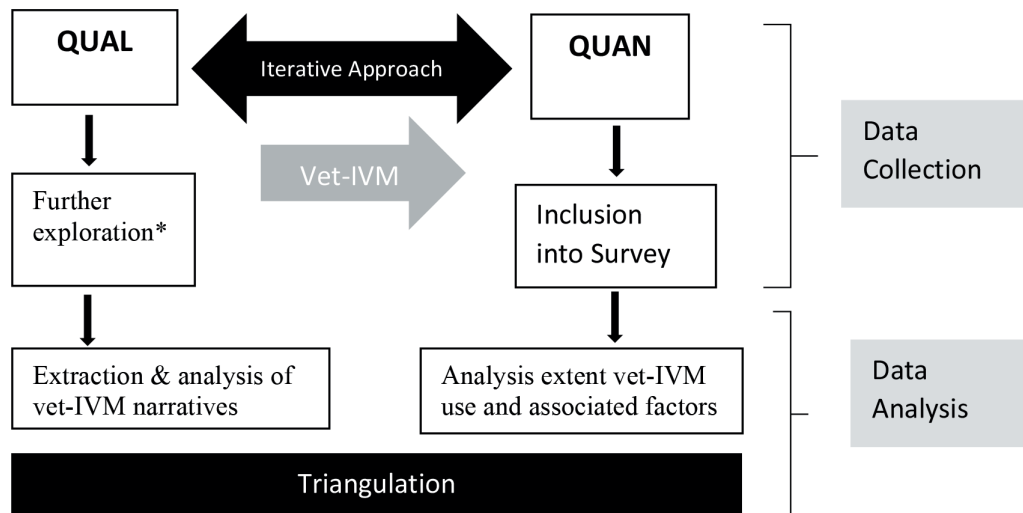


Figure 1 Mixed-methods convergent design using parallel data collection with an iterative approach. vet-IVM, veterinary ivermectin. * To further explore the theme on vet- IVM a veterinarian was purposefully sampled. Vet- IVM was not brought up purposefully in other qualitative interviews in order to assess its relevance compared to other treatments.

Bolivia. The overall aim of the original study was to gain a holistic overview of the CD-related situation in Monteagudo and to explore CD-related knowledge, attitudes, priorities as well as prevention and treatment behaviour in order to plan community-directed interventions. The study used a convergent design including a household survey, as well as qualitative in-depth interviews (IDI) and focus group discussions (FGD). An iterative approach during data collection allowed for further exploration of emerging topics,²⁷ such as the use of vet-IVM against CD (see also figure 1 and online supplemental file 1). We used methodological, data and investigator triangulation to increase the validity of our results.²⁸

Data collection

For the household survey, a multistage stratified random sampling procedure was applied, covering approximately 10% of the municipalities' households, while maintaining their proportional distribution (see also table 1 and online supplemental file S1). One adult member per household was eligible to participate. Qualitative interviews were conducted with patients with CD, relatives and key informants. Qualitative participants were selected purposefully or by snowball sampling (see also online supplemental file S1).

The widespread use of vet-IVM was a surprising theme that emerged during several initial patient and key informants' interviews. We therefore included self-reported vet-IVM use within the survey to determine its extent in the context of an iterative approach (see also figure 1). Several participants cited vet-IVM spontaneously as preventive measure against CD. We moreover further explored vet-IVM use during qualitative data collection by purposefully sampling a veterinarian. In other qualitative interviews, we did not specifically address vet-IVM use, but waited to see if participants would talk about

it spontaneously to understand its importance in the context of Bolivia's system of medical pluralism¹⁶ (see also table 1).

Data extraction and analysis on vet-IVM use against CD

A total of 669 household members from 26 communities participated in the survey. No household refused participation. Moreover, 14 IDI and 2 FGD were conducted (table 2 depicts the sociodemographic characteristics of the survey population; the overall results have been reported elsewhere²⁵).

Qualitative analysis

We extracted all narratives related to vet-IVM intake against CD using NVivo V.12. The primary focus was to understand the phenomenon of unscientific vet-IVM use, its extent and importance among other treatment options, as well as potential underlying factors. Content analysis with a content-structuring methodology approach aligned to the study by Kuckartz²⁹ was performed by two independent female researchers (SP/JZ, both medical doctors) using consensual coding. First, narratives on vet-IVM were read several times, focusing on manifest and latent content. Main themes and subcategories were then derived deductively-inductively and case summaries served as an intermediate step for analysis.

Quantitative analysis

For quantitative analysis, we extracted survey data on self-reported vet-IVM use as well as the mentioning of vet-IVM in questions related to preventive behaviour.

Self-reported vet-IVM intake against CD was used as a dependent variable after dichotomisation (1=yes, 0=no/do not know) using the survey question: "have you taken (veterinary) ivermectin against CD?" Independent variables of interest were sociodemographic characteristics, information sources on CD, attitudes regarding the

Table 1 Overview of data collection and extraction for in-depth analysis of vet-IVM use against CD

	Household survey	Qualitative interviews
Inclusion criteria	<ul style="list-style-type: none"> ▶ At least 18 years old ▶ Resident municipality of Monteagudo ▶ One participant/household 	<ul style="list-style-type: none"> ▶ At least 18 years old ▶ Belonging at least to one of three groups: <ol style="list-style-type: none"> 1. Patient with CD 2. Relative of patient with CD 3. Key informant (eg, health staff, traditional healer, member of national CD programme, veterinarian, PIV*)
Exclusion criteria	<ul style="list-style-type: none"> ▶ Not present at the moment of study ▶ No informed consent given 	No informed consent given
Sampling procedure	Multistage-stratified randomised sampling procedure: <ol style="list-style-type: none"> 1. Stratification of all households into 17 health centre strata 2. Calculation of households to include/stratum (proportional) 3. Random selection of communities 4. Random selection of households 	<ul style="list-style-type: none"> ▶ Purposeful sampling ▶ Snowball sampling
Total sample	669 survey participants from 26 communities (9.8% of all households of Monteagudo municipality)	14 in-depth interviews 2 focus group discussion (1 among young adults, 1 among health staff)
Data extracted on vet-IVM	<ul style="list-style-type: none"> ▶ Outcome: self-reported use of vet-IVM against CD ▶ Exposure variables of interest† ▶ vet-IVM mentioned as preventive method against CD 	Narratives focusing on vet-IVM from: <ul style="list-style-type: none"> ▶ 8 in-depth interviews ▶ 2 focus group discussions ▶ 1 in-depth interview with a veterinarian focusing on vet-IVM use against CD

*PIV: community volunteers responsible for vector surveillance.

†Exposure variables of interest: sociodemographic variables and other social determinants of health (eg, rurality, community access to electricity, presence of vectors, reported health access barriers), community and health centre strata, elements aligned to PMT, CD status, self-reported physical and emotional health status, number of symptoms potentially caused by CD.
 CD, Chagas disease; PIV, Puesto de informacion vectorial; PMT, Protection Motivation Theory; vet-IVM, veterinary ivermectin.

disease and treatment options (aligned to protection motivation theory) as well as potential health system barriers to treatment and other social determinants of health.

The bivariate results were computed using Fisher's exact test to determine whether a statistically significant difference existed between the preselected reference group (eg, age group 18–25 years, indicated with 1 in the OR column in [table 3](#)) and each of the other groups (eg, age groups 26–40 years, 41–60 years, etc) with respect to their use of vet-IVM for each variable of interest. Exposure variables associated with vet-IVM use with a p value=0.1 were included into multivariate analysis. The multivariate results were computed by fitting a logistic regression to the data. In order to account for potential clustering within the data, we calculated robust SEs using the HC3 estimator.³⁰ Very small groups had to be merged with their neighbouring categories. An association with a p value of <0.05 was considered significant. Finally, we used the Cochran-Armitage test to determine whether any statistically significant trends existed with respect to vet-IVM use for each of the ordinal variables in the data.

All quantitative results were computed in a Jupyter Notebook environment using Python (V.3.8.5). The *stats* Package from the *SciPy* library (V.1.21.0) was used

to compute Fisher's exact test, and the *statsmodels* library (V.0.12.1) was used to fit the logistic regression model and perform associated statistical tests, as well as for the Cochran-Armitage test for trend.

Patient and public involvement

The study was part of a baseline assessment aimed at targeting future interventions to the communities' priorities, knowledge and experiences with former projects. Patients and their relatives participated in all phases of this study, from the planning to the dissemination of results. Because of the high CD prevalence (approximately 46% among adults), there was an overlap between being a patient or relative and being involved as key informant or project staff. In order to assure confidentiality of local participants and key informants, no detailed socio-demographic characteristics will however be presented and not every CD infection will be disclosed.

RESULTS

Qualitative results

Vet-IVM use against CD was discussed in nine IDI and two FGD which were therefore included in the current analysis. These interviews consisted of 21 participants (11

Table 2 Sociodemographic characteristics of the survey population

Gender*	N=669 (%)
Female	412 (61.8)
Male	255 (38.2)
Age group (years)*	N=669 (%)
18–25	95 (14.2)
26–40	176 (26.3)
41–60	248 (37.1)
61–93	147 (22.0)
Highest educational level*	N=669 (%)
Incomplete schooling	420 (62.8)
Complete secondary school	120 (18.0)
Tertiary	62 (9.3)
Academic	63 (9.5)
Profession*	N=669 (%)
Household	275 (41.4)
Farming	151 (22.7)
Student	47 (7.1)
Teacher	38 (5.7)
Job within healthcare†	22 (3.3)
Other	131 (19.7)
Health insurance*	N=669 (%)
Yes	232 (34.7)
No	436 (65.3)
Source of information on CD	N=669 (%) ^{MC}
Healthcare centre	295 (44.1)
Health campaign	233 (34.8)
Experience of someone close	215 (32.1)
Family	204 (30.5)
Hospital	182 (27.2)
Radio/TV	155 (23.2)
School	87 (13.0)
Social media	21 (3.1)
Have children*	N=669 (%)
Yes	548 (81.9)
No	108 (16.1)
Tested for CD	N=669 (%)
Yes	511 (76.4)
No	153 (22.9)
Do not know	5 (0.7)
CD serology result*	N=511 (%)
Positive	236 (46.3)
Negative	248 (48.6)
Do not know	26 (5.1)

*Non-respondents: gender=2 (0.3%), age=3 (0.5%), education=4 (0.6%), health insurance=1 (0.2%), profession=5 (0.7%), having children=13 (1.9%), CD serology result=1 (0.2%).

†Job within healthcare included health staff and people sought for professional advice on CD (including traditional healers, pharmacists and veterinarians).

CD, Chagas disease; MC, multiple choice.

females) aged 18–70 years. Educational level ranged from no education to academic education. A total of three IDI participants did not have health insurance. CD status ranged from asymptomatic to severe heart failure in need of a pacemaker. Reported professions included subsistence farmers, housekeepers, teachers, students, traditional healer, veterinary doctor, medical doctors, nurses, driver and cleaner.

Five main themes were identified: (1) the extent of the vet-IVM phenomenon, (2) the perception of vet-IVM as a treatment for CD, (3) the vet-IVM market and the controversial role of stakeholders, (4) concerns about potential adverse events and (5) underlying factors of vet-IVM use against CD (the coding framework can be found in online supplemental material S1 and additional verbatims (VS1–VS16) in online supplemental material S2).

Theme 1: the extent of the vet-IVM phenomenon

vet-IVM was mentioned as one option for the prevention and cure of CD, extensively used during the last two decades (VS1–VS5, VS8–VS9). Several participants reported own vet-IVM use. It was mainly consumed orally, dispersed in water or milk, adjusted to weight (VS3, VS5) and at times combined with other alternative or biomedical treatments (VS6, VS7).

I have seen injectable Ivermectin being used (against CD). It is not injected, but consumed dissolved in water. Even I took it, because I knew that I had CD[...] I have seen the majority of people buying it. (FGD, female healthcare (HC) worker)

Theme 2: the image of vet-IVM as a treatment for Chagas disease

An image of a ‘wonderdrug’ emerged during narratives. Participants had heard stories about people diagnosed with advanced CD being spontaneously cured. The frequently used term ‘deparasitic’ underlined ivermectin’s image as a potent drug with the ability to clean the (animal) body of all types of parasites (VS1, VS2). There were however also patients that expressed their doubts about its effectiveness, and potential adverse events (VS4, VS5).

Her husband was told that he was about to die, he couldn’t work anymore, or anything. She heard about it (vet-IVM) from other people and told us: ‘I took a syringe of 2 ml and gave ivermectin to my husband. He was completely cured and now he works again’.

It might be because of ivermectin that I killed Chagas. Because it kills every beast. That’s what happens with the cattle too, it kills all the beasts. (Male patient and community leader)

I heard from a man, a friend of a close friend of our family [...]. He already suffered from pain in his heart, couldn’t breathe etc. And after treatment with Ivermectin he said ‘I am feeling fine. My doctor said

Table 3 Side-by-side display of quantitative and qualitative results of factors related to the use of vet-IVM against CD

Categories	N (%)	Unadjusted (bivariate)			Adjusted (final model)			Verbatims
		OR	95% CI	P value	aOR	95% CI	P value	
Gender								
Male	255 (38.2)	1			1			"It's more common among older people. Most of their children have already graduated from school, gone to university where they learn that there are medications for human use, free of charge. But those with the old beliefs: it is all about what helped his comrade. He will take what helped his fellow". (Veterinarian)
Female	412 (61.8)	0.82	0.55 to 1.23	0.35	0.85	0.21 to 1.43	0.218	
Age group (years)								
18–25	95 (14.2)	1			1			
26–40	176 (26.3)	4.15	1.21 to 14.31	0.01	6.25	0.58 to 17.36	0.182	
41–60	248 (37.1)	8.54	2.6 to 28.02	<0.001	12.17	0.94 to 26.95	0.059	
61–93	147 (22.0)	11.46	3.43 to 38.29	<0.001	17.01	1.24 to 36.55	0.027	
Education								
Incomplete schooling	420 (62.8)	1			1			
Complete schooling	120 (18.0)	0.5	0.28 to 0.9	0.02	0.49	0.29 to 1.56	0.356	
Tertiary	62 (9.3)	0.52	0.24 to 1.13	0.13	0.54	0.15 to 2.45	0.475	
Academic	63 (9.5)	0.12	0.03 to 0.48	<0.001	0.12	0.01 to 0.78	0.029	
Information sources								
Experience of someone close	215 (32.1)	2.77	1.85 to 4.14	<0.001	3.13	1.62 to 5.02	<0.001	"In Santa Cruz a man told me: 'you are not going to get cured. You'll be at the hospital in vain.[...] Leave and take Ivermectin!' [...] Back home happened the same thing, again and again, until I took it". (Older women, advanced CD)
Elements aligned to protection motivation theory								

Continued

Table 3 Continued

	Unadjusted (bivariate)		Adjusted (final model)		Verbatims				
	Categories	N (%)	OR	95% CI		P value	aOR	95% CI	P value
Perceived effectivity of health system to care for CD	Strongly disagree	16 (2.4)	1		1				"CD (serology) doesn't become negative right away. This is why a lot of people have already taken Ivermectin. Because of the long time it takes for the test (serology) to get negative. They don't believe much in the effectiveness of benznidazole". (Rural physician)
	Disagree	60 (9.0)	1.44	0.36 to 5.77	0.748	1.35	0.06 to 4.83	0.572	
	Uncertain	86 (12.9)	1.07	0.27 to 4.17	1	1.07	0.06 to 5.21	0.621	
	Agree	408 (61.0)	1.01	0.28 to 3.62	1	0.95	0.09 to 6.11	0.773	
	Strongly agree	99 (14.8)	0.38	0.09 to 1.62	0.181	0.38	0.02 to 1.88	0.15	
Self-rated health and disease status									
Health status	Very good	22 (3.3)	1		1				"It's both: people that are sick and have been diagnosed by laboratory and people that don't want to get sick, because there might be people affected (by CD) within the family. So, everyone takes it (Ivermectin) to prevent". (Veterinarian)
	Good	312 (46.6)	1.3	0.29 to 5.81	1	1.26	0.01 to 4.28	0.324	
	Fair	311 (46.5)	2.96	0.68 to 12.96	0.183	2.81	0.01 to 5.01	0.374	
	Bad	22 (3.3)	6.92	1.29 to 37.29	0.034	7.5	0.06 to 16.61	0.769	
	Very bad	1 (0.1)	Inf	-	-	Inf			
Emotional health status	Very good	25 (3.7)	1		1				"I went to all the doctors, then to a company who make medicines, they sell herbs, powders, solutions [...]. After that I took Ivomec". (Older woman, advanced CD)
	Good	308 (46.0)	0.88	0.25 to 3.1	0.742	0.85	0.06 to 16.61	0.99	
	Fair	311 (46.5)	2.37	0.69 to 8.14	0.221	2.81	0.09 to 25.16	0.782	
	Bad	22 (3.3)	2.16	0.45 to 10.32	0.446	7.5	0.02 to 9.10	0.574	
	Very bad	2 (0.3)	Inf	-	-	Inf			

Continued

Table 3 Continued

	Categories	N (%)	Unadjusted (bivariate)		Adjusted (final model)		Verbatims		
			OR	95% CI	P value	aOR		95% CI	P value
Self-reported number of chronic symptoms	0	384 (57.4)	1		1		"My colleagues tell them: take this antiparasitic drug for your cow and while you're at it: take some 5-6 mL for yourself. It's good against CD. Like, just as prevention-without knowing if the person is sick". (Veterinarian)		
	1	108 (16.1)	1.77	1.02 to 3.05	0.047	1.77		0.60 to 2.65	0.543
	2	81 (12.1)	1.36	0.71 to 2.61	0.378	1.16		0.20 to 1.64	0.295
	3	41 (6.1)	3.39	1.67 to 6.88	0.002	3.49		0.50 to 3.39	0.595
	4	30 (4.5)	2.8	1.21 to 6.45	0.026	2.36		0.23 to 2.42	0.617
	5	19 (2.8)	3.81	1.43 to 10.12	0.011	3.93		0.34 to 5.31	0.672
6	6 (0.8)	6.53	0.9 to 47.39	0.092	6.73	0.06 to 64.36	0.684		
Test result of CD serology	Negative	236 (46.3)	1		1				
	Positive	248 (48.6)	4.07	2.42 to 6.86	<0.001	3.89	1.39 to 6.20	0.005	
	Do not know	26 (5.1)	1.92	1.04 to 3.53	0.039	1.68	0.23 to 9.16	0.683	
	Never tested	158	3.08	1.12 to 8.48	0.035	1.8			
Perceived HC barriers in CD treatment									
Unavailability of biomedical treatment	No	140 (20.9)	2.14	1.38 to 3.31	0.001	2.3	1.45 to 5.18	0.002	
	Yes	96 (14.3)	1.77	1.07 to 2.94	0.031	1.8	0.65 to 2.79	0.425	
HC barriers encountered	Yes	99 (14.8)	1		1		"Patients come here and ask for Ivermectin.[...] If there is no benznidazole, they have to try other things. What they really want is to get treated". (Female nurse)		
	No	514 (76.8)	0.67	0.4 to 1.14	0.147	0.66		0.63 to 3.00	0.431
Did not try to access HC	Yes	56 (8.4)	1.28	0.6 to 2.73	0.559	1.23	0.87 to 8.46	0.086	
	No	514 (76.8)	0.67	0.4 to 1.14	0.147	0.66	0.63 to 3.00	0.431	

Values in bold: P <0.05 (statistically significant).

aOR, adjusted OR; CD, Chagas disease; HC, healthcare; Inf, Infinite; vet-IVM, veterinary ivermectin.

that I don't have any disease anymore'. (Female patient and HC worker)

Local HC workers partially believed in the effectiveness of vet-IVM against CD (VS5, VS10–VS11). Even though they were often aware about the lack of scientific evidence, their narratives at times indicated a belief that vet-IVM might have a (yet unproven) effect.

It seems that someone took Ivermectin and told that prior to treatment he was Chagas (sero) positive and then [...] a while after treatment, the test turned out negative. That is what this person says, but in reality, scientifically we can't know. [...] What we would need is to take a CD positive patient as reference, treat him with ivermectin and after a while re-do the serological test. To see what results we get. To be scientifically sure if the medication had an effect or not'. (Female patient and HC worker)

Theme 3: the vet-IVM market and the controversial role of stakeholders

In addition to self-medication, vet-IVM is administered by a wide array of professionals, such as veterinarians, traditional healers, private practitioners and physicians working in public facilities (VS6, VS10, VS11, VS16). Although many HC workers sought to offer a treatment option to their patients, concerns about unethical commercial interests were also raised. The lack of formal information for veterinarians on this subject as well as on human CD was raised as a concern, because of the important role they play in treatment decisions, especially in remote areas.

There is always a controversy between colleagues (veterinarians). Some think that it is good and others don't. [...] We have never handled this topic at a congress or within a meeting.

I consider it more a business that they have constructed, playing with people's feelings: Playing with CD, because we know that a lot of people in this zone suffer from it. (Veterinarian)

Theme 4: concerns about potential adverse events

Key informants expressed concerns regarding potential adverse events, related to the lack of data, dosage and the use of veterinary formula. Some participants reported adverse outcomes, although direct association with vet-IVM and dosage remained unclear (VS13–VS15), in particular due to the lack of follow-up.

We don't know the pharmacological functioning of this medication within the human body, because it was obviously designed for other species [...] There are associated risks that lead to problems that we will see in the long run. (Urban physician)

There is no follow up. Who would take the responsibility, knowing that it was an animal product administered to humans? (Veterinarian)

Theme 5: underlying factors of vet-IVM use against Chagas disease

Social determinants associated with vet-IVM intake in qualitative analysis were poverty, distance from infrastructure, lack of education, old age and barriers to health information, prevention and care and were also connected to being an easy target for unethical practices. The experiences of other community members were often decisive for making treatment decisions. The lack of availability of BNZ (prior to the introduction of decentralised treatment, and due to BNZ frequently being out of stock), its perceived strong adverse effects, the need for long-term administration and a lack of a perceived effectiveness were linked to the use of vet-IVM. vet-IVM was taken at different disease stages as well as for prevention. Patients with advanced CD had often tried several treatments. Being a parent and fearing having to leave one's children as orphans was also linked to the trial of several different treatments (narratives on underlying factors are summarised side by side with quantitative results in [table 3](#)).

Survey results

Participants' ages ranged from 18 to 93 (mean 46.1). There were 61.8% female and 38.2% male participants. Most participants had been tested for CD (76.4%) and the self-reported prevalence was 46.2%. For detailed descriptions of the included participants and communities, please refer to [Parisi et al.](#)²⁵

Among survey participants, 17.9% (120/669) of all household representatives and 28.4% (67/236) of those who were seropositive for CD reported having used vet-IVM as prevention or treatment against CD (additionally, three people did not know if they had taken vet-IVM). In comparison, only 17.8% (42/236) had completed first-line treatment with BNZ. Moreover, vet-IVM was mentioned as a preventive method by 16.3% (109/669) of survey participants.

Bivariate analysis

Factors associated with vet-IVM intake in the bivariate analysis are summarised in [table 3](#) and online supplemental file S3. Education, age, decreased emotional and physical health status and the perception that biomedical treatment with BNZ had strong side effects showed an effect on vet-IVM intake. In total, 285 patients (42.5%) reported one or more chronic symptoms compatible with CD and an increased number of symptoms was related to vet-IVM intake. On the other hand, the perceived effectiveness of local health facilities to provide adequate care for CD showed a decrease with vet-IVM intake ([figure 2](#)). There was no association between the use of vet-IVM and BNZ.

Multivariate analysis

In the multivariate analysis, being above 60 years old, being diagnosed with CD and the unavailability

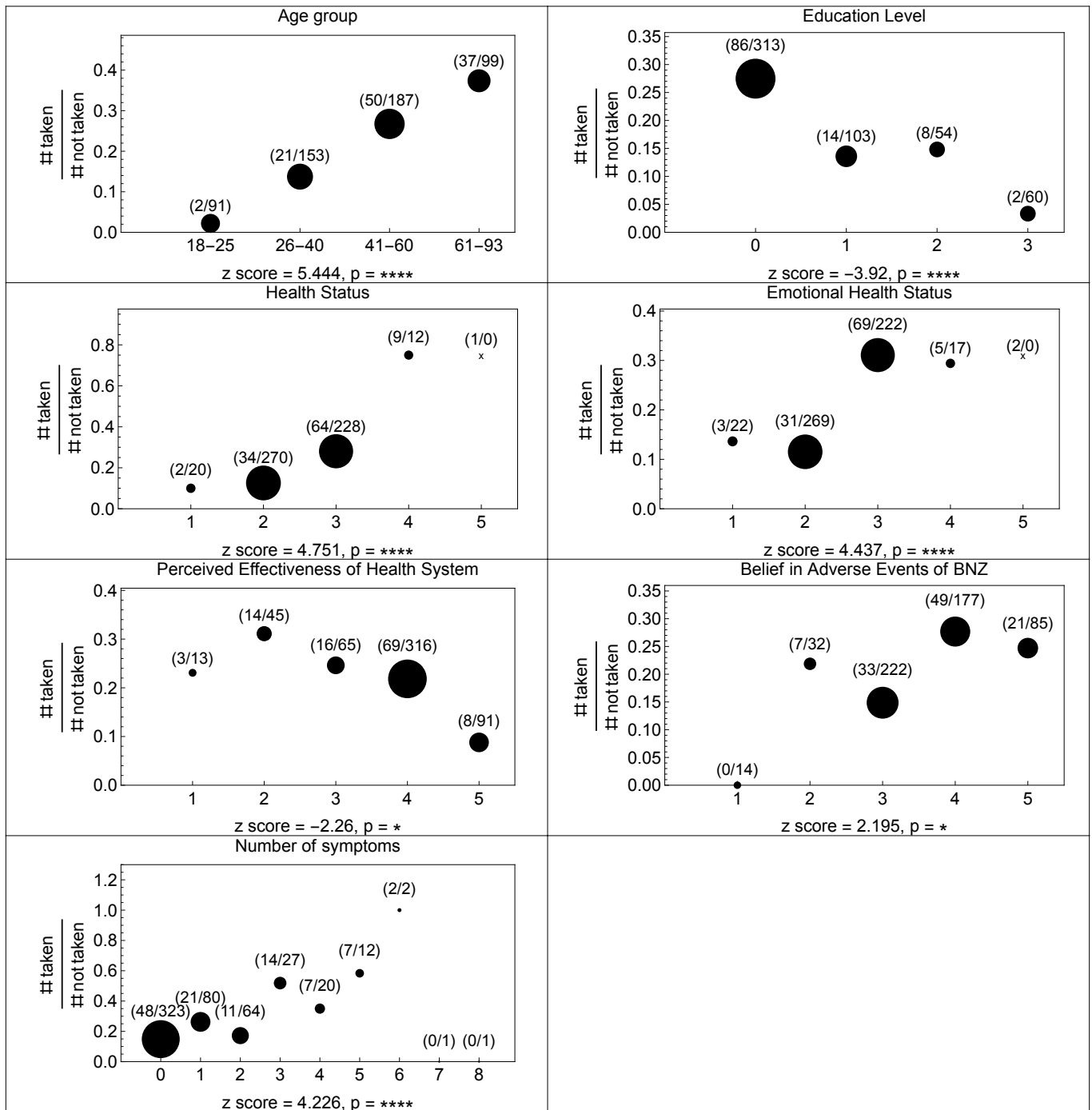


Figure 2 Bivariate analysis on factors associated with veterinary ivermectin intake, test for trend. Variable categories: education 0=no/incomplete schooling, 1=complete schooling (secondary), 2=tertiary education, 3=academic. Health status and emotional health status 1=very good, 2=good, 3=fair, 4=bad, 5=very bad. Perceived effectiveness of health system: responses to the question “If I go to the health center, I will get all the help I need to get cured”. Belief in adverse events of benznidazole (BNZ): responses to the question: ‘The treatment has strong negative effects’, both assessed on a 5-point Likert scale 1=strongly disagree, 2=disagree, 3=uncertain, 4=agree, 5=strongly agree. ns, $p>0.05$; * $0.01<p<0.05$; ** $0.001<p<0.01$; *** $0.0001<p<0.001$; **** $p<0.0001$.

of biomedical treatment were significantly associated with the intake of vet-IVM against CD. Participants with increased education were less likely to report vet-IVM intake, but only academic education reached statistical significance. The experience of other community members as information sources played a significant role in the decision to be treated with vet-IVM. Table 3 displays a summary of the main factors associated with vet-IVM intake in quantitative and qualitative interviews (the complete table can be found in online supplemental material S3).

DISCUSSION

This is the first study exploring underlying factors of unscientific vet-IVM use against CD. The results serve to derive similarities in light of vet-IVM hype during the COVID-19 pandemic.

Our study highlights that vet-IVM has played a major role in the prevention and treatment of CD for several years. Although its use against CD had been documented before,¹⁶ the extent of the phenomenon was a surprising finding. vet-IVM use was reported by 18% of total and 28% of survey participants seropositive for CD and exceeded BNZ intake. There was no association between vet-IVM and BNZ intake, indicating that both were rather complementary than competing treatments. vet-IVM often formed part of a ‘pragmatic multiple strategy’ previously described in Bolivia, which included self-medication alongside traditional and biomedical treatment options.³¹ Increasing age, lack of education, unavailability of BNZ and the experience of someone close were underlying factors for vet-IVM intake.

In line with findings from other countries,³ ivermectin had an excellent reputation among communities. vet-IVM’s broad spectrum against endoparasites and ectoparasites led to a perceived ability to ‘clean’ animal and potentially human bodies of all kinds of germs. An image of a ‘wonderdrug’ emerged in several narratives, a term also used by some scientific authors when referring to ivermectin and its potential efficacy against yet undiscovered diseases.^{132–35} The hope that (veterinary) ivermectin might be effective against CD was also reflected in narratives among HC workers, despite their awareness on the lack of scientific evidence.

vet-IVM had been distributed against CD by a wide range of influential stakeholders for almost two decades, indicating that the belief in its effectiveness might be strongly anchored in the region. Some key informants however raised concerns about unethical, economically motivated vet-IVM administration and adverse events potentially related to overdosage and veterinary formulations, which are not designed for humans and have never been assessed in trials. A recent systematic review concluded that serious adverse events cannot be ruled out when ivermectin is administered at higher doses.³⁶

Underlying factors resulting from the triangulation of qualitative and quantitative results were lack of education

and advanced age. Although vet-IVM was also taken to prevent CD, a CD diagnosis and a decreasing health status were related to trial and error of different treatments, including vet-IVM. Barriers to health access also played a role and were connected to misinformation and vulnerability to unethical practices in qualitative analysis. Narratives of community members often centred around stories of spontaneous healing and played a fundamental role in treatment decisions. In line with findings from the USA,³⁷ especially older patients relied on their friends’ advice for health decisions.

Several factors connected to vulnerability in our study have also been linked to COVID-19-related morbidity, such as old age, lack of education and access barriers to HC and information.^{38–41} Indigenous populations are often vulnerable to CD and considered at special risk for COVID-19 complications.^{42 43} Although CD is not systemically assessed as a comorbid condition and therefore invisible in death statistics, it could also directly contribute to COVID-19-related mortality among Latin-Americans, with an estimated 1 million people suffering from CD-related cardiac manifestations.^{12 44–46}

Implications for the COVID-19 pandemic

The extent of the phenomenon, the existing vet-IVM market and ivermectin’s widespread image as ‘wonderdrug’ against CD, a disease often associated with despair, might have contributed to its premature proclamation as a cure against COVID-19, when initial *in vitro* experiments suggested a potential effect. In the absence of accessible options, health professionals and vulnerable communities can easily project their hopes into ivermectin’s ‘yet’ unproven efficacy against CD and COVID-19. Perez-Garcia *et al*, for instance, call for repurposing ivermectin to tackle multiple diseases affecting Venezuela’s population and in this context name ivermectin’s potential efficacy against malaria, CD, arboviruses, *Leishmania* and SARS-CoV-2.⁴⁷

According to current evidence, ivermectin is however not recommended against SARS-CoV2.^{6 7 48} Indiscriminate use of ivermectin is problematic due to environmental concerns^{49 50} and because it hinders high-quality trials on its effectiveness.⁵¹ Other concerns are the lack of follow-up on complications, especially when using vet-IVM and off-label treatment of severely ill patients with COVID-19. A hyperinflammatory state might lead to severe neurotoxicity caused by ivermectin, which is usually prevented from passing to the central nervous system by an intact blood-brain barrier.¹⁹ Moreover, individuals with specific gene mutations may have adverse reactions.⁵²

In light of the COVID-19-related infodemic, our study highlights that special emphasis should be on vulnerable communities to make this updated information available and to foster resilience against circulating misinformation.^{53 54} NTDs are considered indicators for health (in) equity and could help to identify communities most in need of interventions.^{55–59}



Promoting health literacy and adequate dissemination tools, such as audio-based interventions for illiterate community members, could reduce their chances of becoming an easy target for unethical practices.^{60–62} Effective education messages should be in easy-to-understand language, built on local knowledge and include circulating health information. Their design and dissemination should be participatory,^{60–62} including communities and all relevant stakeholders such as HC worker, traditional healers, pharmacists and also veterinarians, who can play an important role distributing vet-IVM.^{63 64}

Finally, as shown in our study, the misuse of inadequate treatment is caused by the unavailability of real options. In case of CD, there is an urgent need for better and faster working treatments and to assure accessibility of existing treatments. In the case of COVID-19, global solidarity is needed to assure equity of access to potential future treatments and vaccinations to prevent COVID-19 from becoming the ‘newest serious NTD in the region’.⁶⁵

This is the first study exploring the phenomenon of unscientific vet-IVM use against CD and underlying factors. There were however also some limitations: (1) the study was conducted in one Bolivian municipality at the end of 2018, in the pre-COVID-19 era. Although we tried to discuss some potential similarities, the current COVID-19 situation might be very different and our results cannot be generalised to other regions; (2) there was an over-representation of females during the survey, which were more often encountered at home during daytime; (3) vet-IVM was a theme that emerged during qualitative data collection and was integrated in the survey, in line with an iterative approach. Apart from the purposeful interview with a veterinarian, we did not bring up vet-IVM, but waited if the topic was spontaneously addressed to understand its importance in the context of different treatment options. Participants not talking about vet-IVM might therefore have a different opinion or attribute less importance to the topic and it was difficult to assess data saturation. We however tried to mitigate this effect by analysing contrasting viewpoints during qualitative analysis. We moreover believe that the triangulation of several data sources (qualitative: participants spontaneously talking about vet-IVM, own vet-IVM intake, narratives of patients and key informants about the vet-IVM extent; quantitative: self-reported vet-IVM, citing vet-IVM as preventive measure) allowed an overall understanding of the extent and importance of the vet-IVM phenomenon.

CONCLUSION

This is the first in-depth study on the extent and underlying factors of vet-IVM against CD. Although the results cannot be generalised to other settings, they serve to discuss potential similarities in light of the widespread use of vet-IVM during COVID-19. Our results highlight the pre-existing importance of unscientific vet-IVM intake. Social determinants of health, the unavailability

of effective treatment options and circulating rumours may be underlying factors of the phenomenon. In times of increased vulnerability, local and international stakeholders should put specific attention on communities with high NTD burdens, such as CD. Continuing the work to engage and empower neglected communities can help to protect them from fake news and unethical practices, such as the indiscriminate use of vet-IVM.

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