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ORIGINAL RESEARCH

Survey to evaluate the proficiency in the use of antibacterial drugs in shrimp farming in the state of Sonora, Mexico

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Abstract

Antibiotic drugs (ABD) are often used in shrimp farms to treat the disease when a bacterial diagnosis is presumed. This scenario was the impetus to carry out a field survey to define how ABD are employed in the State of Sonora, the second largest producer of shrimp in Mexico. Twenty-nine farms were surveyed through their general managers. According to interviews conducted, the most frequent bacterial diseases that were treated with antibiotics in 2020 were: Acute Hepatopancreatic Necrosis Disease (65%), vibriosis (51%), and Necrotizing hepatopancreatitis bacterium (41%). The most common ABDs were enrofloxacin, oxytetracycline and florfenicol, and drug preparations employed were often intended for non-aquaculture species, mainly poultry, and pigs. The main criteria for selecting a given antibiotic was a direct recommendation, followed by the market price. Neither pharmacokinetics nor pharmacodynamics nor harvesting withdrawal time were taken into account. The absence of protocols to safeguard the health and integrity of workers was detected, training programs for the responsible use of ABD were not encountered, and no data on bacterial resistance to ABD is available in this region. It is concluded that at least formal studies to define the pharmacokinetics of antibiotics are needed to rationalize their use in shrimp production.

KEYWORDS
antibacterial-drugs, pharmacology, shrimp-farming, Sonora-Mexicosurvey

1 | INTRODUCTION

The production of shrimp in Mexico reached 127,800 tons in 2016 (FAO, 2018) and 189,000 in 2020 (FAO, 2022). That is a 47% increment in the production of this crustacean. However, the progress of this activity could have been more significant as it was considerably hindered by the occurrence of various viral diseases such as the Taura syndrome Virus (TSV) (SENASA, 2020), the White-Spot syndrome Virus (WSSV) (Hasson et al., 2006; Peinado-Guevara & López-Meyer, 2006), the Infectious Hypodermic and Hematopoietic Necrosis Virus (IHHNV) (López-Téllez et al., 2015; Macías-rodríguez et al., 2014), and due to outbreaks of bacterial diseases such as those produced by *Aeromonas hydrophila* (Zhou et al., 2019), *Pseudomonas* spp. (Gómez-Gil et al., 2010), and mainly due to bacteria of the genus *Vibrio* that is, *V. harveyi*, *V splendidus*, *V. alginolyticus* and particularly *V. parahaemolyticus* (Finkelstein & Oren, 2011; Haenen et al., 2013; Leaño, 2016; Parmar & Yusufzai, 2018). Some of these bacteria can synthesize two types of toxins (A and B) that attack the hepatopancreas (Kumar et al., 2021). In particular, *V. parahaemolyticus* is the leading causative agent of the so-named acute necrosis of the hepatopancreas or early mortality syndrome (AHPND or EMS) (Leaño, 2016; Soto-Rodriguez et al., 2015).

Prevention and biosafety strategies have been implemented to control the spread of bacterial diseases, such as some operating manuals, a program to train workers was established when possible, shrimp-farm installations were improved, sanitary fords were installed, quarantine areas were implemented, and an attempt has been made to limit the acquisition of nauplii, post larvae (PL), or larvae, only from farms certified as pathogen-free, as laid out by the official Mexican Standard (Ley General de Pesca y Acuacultura Sustentables) (SENASICA, 2015); particularly regarding pathogens of mandatory notification (Boyd et al., 2005; Cuellar-Anjel et al., 2010). These disease prevention and containment strategies have achieved considerable success. However, there are still shrimp health issues that need to be addressed. For instance, some bacterial strains have been regarded as resistant to specific antibiotics (Hossain et al., 2021). Hence, their success in treating bacterial disease outbreaks has been moderate.

Furthermore, the commercial approval of some of ABDs for shrimp is pending (Cock et al., 2009; Munang'andu, H. M., Mutoloki, S., & Evensen, O., 2016). As an alternative to the use of ABDs, the administration of probiotics in the shrimp diet has also been attempted, particularly to prevent shrimp diseases. Results can be described as variable at best (Karthik et al., 2014; Wang et al., 2005). Nevertheless, it is feasible to assume that these preventive maneuvers and other non-antibacterial-based approaches may help reduce bacterial and even viral diseases. However, the perception among producers and technicians dedicated to shrimp production is that dosing ABD remains an irreplaceable practice when treating and using them as a metaphylactic procedure to prevent the spread of a bacterial disease.

According to the 2019 Annual Report of the Aquaculture Health Work Program in Shrimp Farms of the State of Sonora (Programa de Trabajo Sanitario Acuícola en Camaroneras del Estado de Sonora), issued by the Aquaculture Health Committee of the State of Sonora (Comité de Sanidad Acuícola del Estado de Sonora) (COSAES, 2020a), this state is ranked as the second largest producer of shrimp obtained by aquaculture. In the registry, 154 Aquaculture Production Units (APU) are dedicated only to shrimp farming, of which 145 remain active to this date Table 1. Together, they add up a total of 26,593 hectares of sowing. Thirty-one APUs carried out a second production cycle

TABLE 1 Productive indices of the State of Sonora, Mexico, in 2019.

Heading	First cycle	Second cycle	Total
Number of APUs	145	31	145[a]
Sown área (ha)	26,593	4474	31,067
Sown density (PL/m^2)	17.7	15.9	17.5[b]
Millions of postlarvae	4713	710	5423

Note: Adapted from COSAES (2020a), (2020b).
Abbreviation: APUs, aquaculture production units.
[a]Total of active APUs.
[b]Weigthed average between the first and the second cycle.

TABLE 2 Productive indices by region within the state of Sonora, Mexico in 2019.

Zone	No. of APUs	Sown area (ha)	Sown density PL/m^2	Million PL
North	33	16,716	17.4	2910
Center	24	2310	23.6	546
South-A	72	9089	16.3	1486
South-B	16	2952	16.2	481

Note: Adapted from COSAES (2020a), (2020b).
Abbreviations: APUs, aquaculture production units; PL, postlarvae.

in 2019. Table 1 shows the latest production data for Sonora in 2019, and Table 2 shows its regional productive indices. Farms that were visited to carry out the survey were described in Figure 1.

The total shrimp production in the state in 2019 was 67,570 tons, with an average of 2.49 tons per hectare, an average shrimp weight of 21.97 g and an average survival rate of 58%. As depicted in Figure 2, shrimp production reached a historical maximum in 2009. After that, a drastic fall is distinguishable, and the emerging disease caused by *Vibrio parahaemolyticus* (AHPND) has been regarded as one of the leading causes. The depression in shrimp production is still easily perceived today (COSAES, 2020b).

In a preliminary survey, the Sonora's State Health Committee (*Comité Estatal de Sanidad Acuícola del Estado de Sonora*, COSAES), and the government agency known as the National Service for Agrifood Health, Safety and National Service for Agrifood Health, Safety and Quality (*Servicio Nacional de Sanidad, Inocuidad y Calidad Agroalimentaria*), SENASICA, concluded that there has been an excessive and often unnecessary use of ABDs to counteract disease outbreaks, empirically regarded as being of bacterial origin (Santiago H., Espinosa P., & Bermúdez A., 2009). This perception has never been supported in most cases. Consequently, no records of the criteria utilized to decide when antibacterial intervention was necessary were found, and the pathogen was rarely identified and characterized. No records of the dose ranges that were selected and the duration of each treatment were not recorded. Furthermore, information on the pharmaceutical form chosen to deliver the antibacterial drug and quantification of its efficacy is also lacking. Of course, determining concentrations of the active principle in shrimp's hemolymph has never been attempted for the available pharmaceutical preparations used in shrimp farming[1] in Mexico.

Given the panorama described on the shrimp-farming industry in Sonora, Mexico, and considering the importance of the correct use of antimicrobials in all human activities and shrimp farming is no exception. There is a real

[1]SENASICA: National Service for Agrifood Health, Safety, and Quality (*Servicio Nacional de Sanidad, Inocuidad y Calidad Agroalimentaria*): Information provided by the Directorate of Aquaculture and Fisheries Health (DSAP), through the Internal Control Office, August 21, 2021;

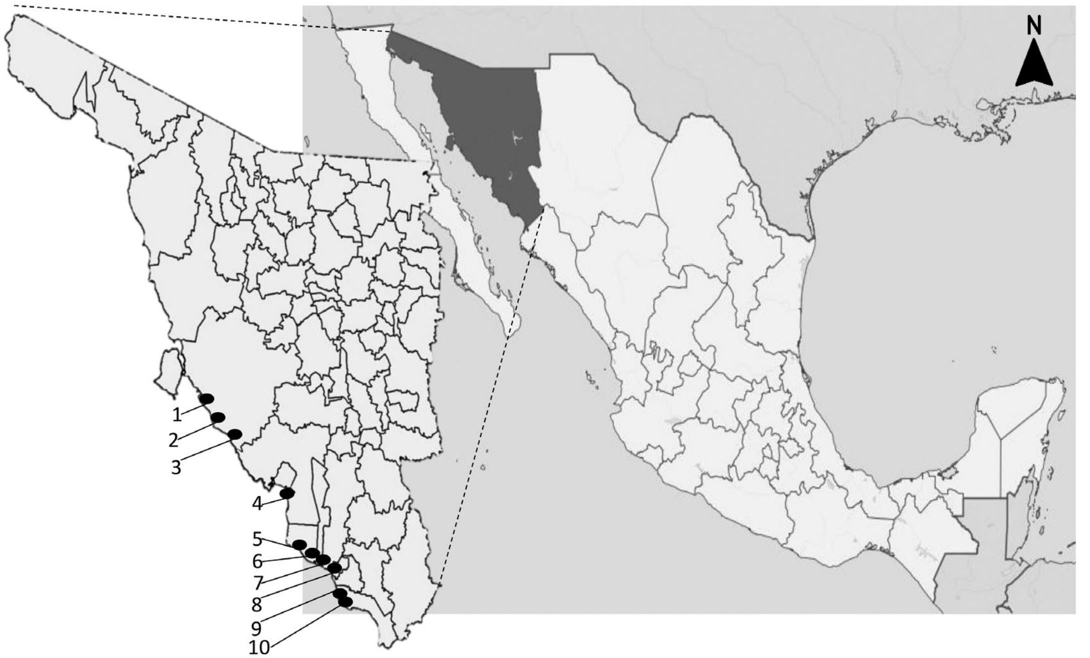

FIGURE 1 Location of the interviewed shrimp production units in the following municipalities in Sonora, Mexico. Bahía de Kino (1), Cardonal (2), Tastiota (3), Cruz de Piedra (4), Lobos (5), Mélagos (6), Atanasia (7), Tobari (8), Siari (9) and Aquiropus (10).

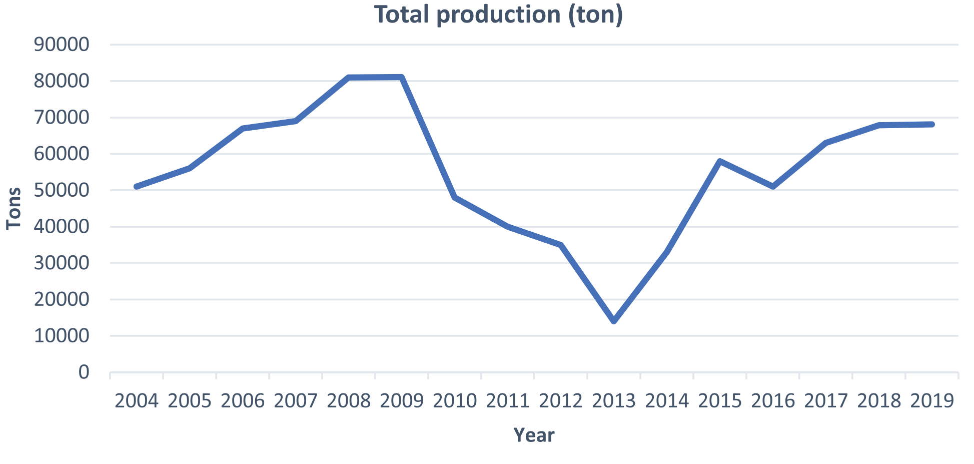

FIGURE 2 Total shrimp production in Sonora, Mexico (2004–2019).

potential impact that antibacterial drug residues may have on the environment, and human health through adverse drug reactions and the generation of bacterial resistance, a systematic survey of how antibacterial drugs are utilized in shrimp farming in the state of Sonora, is of paramount importance.

In this study, the proficiency level was evaluated based on the quantity and quality of theoretical and practical knowledge that a person possesses on the use of antimicrobial drugs, and how these features are utilized to prescribe and practically indicate how to carry out shrimp dosing when affected by a bacterial disease. Proficiency in the use of antibiotics is studied to locate areas of opportunity that may optimize the way antibacterial drugs are used in shrimp. Finally, the question of whether or not these antibacterial drugs are being rationally utilized, must be answered. In addition, such a case study could reveal what information needs to be added to redirect research efforts. Furthermore, economic losses due to product rejection in internal and external markets must be considered necessary. Hence, the objective of this study was to evaluate, through an interview, the prevailing situation regarding the use of antimicrobial drugs in the shrimp farming industry in the State of Sonora and to project the possible environmental impact derived from these drugs.

2 | MATERIALS AND METHODS

2.1 | Overview of the study area

The State of Sonora is located in the northeast of Mexico. The last record indicated 70,000 tons of white shrimp (*Litopenaeus vannamei*) produced in 2020. This is 44.5% of the country's total production. For convenience and as shown in Figure 1, the state is divided into four regions, North, Center, South A, and South B.[2] Shrimp farms, or as known in this region: shrimp-production units (UPAs) are compelled by law to be associated with each of these regional associations, and they all form the so-called COSAES Committee of Aquaculture Health of the State of Sonora, A.C. that is, COSAES (*Comité Estatal de Sanidad Acuícol del Estado de Sonora, A. C.*). Many UPAs have offices in nearby cities such as Ciudad Obregón and Hermosillo, where marketing is intense. Given the long distances between regions, different aquaculture parks have been established. UPAs share water sources, waste channels, and sanitary barriers. Approximately once a month, each UPA is visited by COSAES personnel to monitor disease presentation and to verify compliance with state and federal regulations, and their health program is reviewed. Their certification is validated if a UPA health, status, and production procedures are in order.

2.2 | Selection of farms interviewed and characteristics of the questionnaire-interview

The study sample could not be comprehensive as the access to various UPAs is restrictive, and the possibility of being admitted to carrying out an interview was only possible through the UPAs' technicians due to COSAES professionals' compulsory visit to a given UPA. All these UPAs were solely dedicated to the monoculture of Pacific white shrimp. The questionnaire interview was intended for those person(s) regarded as the responsible party for each UPA and, therefore, in charge of implementing the treatments. Such a person could be the producer-owner and, in some cases, a manager with professional studies in the field. The questionnaire was structured to collect at least the following information from each UPA:

- Farm general characteristics. To assess whether or not there are similarities in farm sizes, planting densities, feedings/day, biomass calculation methods, non-antibiotic products used, years of experience of the personnel in charge, and seniority years of UPAs.
- Diseases. Aimed at gathering information on methods to achieve diagnosis and professionals in charge. Diagnostic tests and tools utilized, the most frequently encountered pathogens, and in general, any information related to the diagnostic process.

[2]From: https://3a8a7ee5-5d43-433f-96c0-5e9181af9642.filesusr.com/ugd/e56b21_415a4731e57b497bb6997bdde1d867bd.pdf. Last consulted on October 23, 2021.

- Treatments. To find out the most common treatments, collect information on the antibacterial drugs used, dose rates, and intervals. Knowledge of the pharmacokinetics/pharmacodynamics ratios (PK/PD) required for a given antibacterial drug, their toxicity, and withdrawal times.
- Method of inclusion of antibacterial drugs into shrimp's feed. Considering that antibacterial drug dosing in farmed shrimp is only carried out through their feed, enquires were made on the methods used to incorporate these drugs into the feed and whether or not the manufacturer's instructions (if any) were followed.
- Training of leaders and employees. Questions were made to assess their ability to safely handle antibacterial products and how empty containers and unused products were discarded.
- Adverse effects. Potentially attributable to antibacterial drugs used on the farm and detected on workers or shrimp, including a lack of clinical efficacy in the latter.

All the participants in this survey became aware of the objectives pursued. The authors of this survey ensured that all shrimp farms managers the anonymous nature of the survey to avoid rejection of the test or receiving evasive answers. Verbal consent to interviews was obtained in all instances. Only one person conducted all interviews to avoid unnecessary variations due to interpersonal trust.

3 | RESULTS

In all, 78 out of 145 farms were visited, and a total of 29 surveys were carried out in May and June, 2021. According to the results obtained, the managers' professional experience was 22.10 ± 6.72 years, and in 91% of the UPAs this person was an Aquaculture Engineer or a Certified Biologist. The rest (9%) were non-professional personnel with working experience in the field, and none had hired a veterinarian. We attempted to divide the surveyed companies into small, medium, and large. Small ones were less than 100 ha in size ($n = 3$; mean surface 37.1 ± 12.9 ha); medium size farms had a working area between 100 and less than 300 ha ($n = 14$; mean surface 178.61 ± 67.4 ha), and large farms are 300 ha or more ($n = 12$; mean size of 522.49 ± 200.2 ha). Regardless of size, the type of production was classified as semi-intensive, with very similar stocking densities, that is, 20.06 ± 3.48 shrimp/m2, and with high salinity water (39.79 ± 2.80 ppt). Farms only produce Pacific white shrimp (*Litopenaeus vannamei*).

Although there are various ways to calculate the shrimp biomass per pond, these have yet to be validated or experimentally regarded as superior (Jimenez & Guerra, 2011). For example, a popular method called “population-based” consists of throwing a cast net of known dimensions a specified number of times (usually 10 times/ha). The organisms captured in each attempt are counted and the mean value is adjusted to the pond's surface area. The values obtained in this way are correlated with daily food consumption. In turn, this is calculated with the feeding tray method, which consists of depositing submersible food-containing trays in the pond. The amount consumed is recorded daily. Based on previous records, the size of the biomass is estimated (Ruiz-Velazco et al., 2010). Due to the above, the size of the biomass is not known with greater precision, and consequently, it is assumed that the dosage of antibacterials implies a critical calculation error in each pond.

3.1 | Diseases reported

The most common diseases mentioned during the interviews are presented in Table 3. Managers and authors of this study generally recognized that bacterial diseases were commonly present on farms and are, in order from highest to lowest frequency, as follows: AHPND or EMS, other vibrioses, and NHP, with at least one outbreak in each one of the surveyed farms (100% incidence). To a lesser extent, farmers reported occasional problems with viral diseases (24% incidence), and only one farm reported problems with parasites, particularly gregarines (Protozoa, Apicomplex), mainly Nematopsis and Cephalolobusgregarious. In all farms, disease monitoring is attempted weekly to respond if needed quickly.

TABLE 3 Diseases present in shrimp in the State of Sonora, Mexico and their distribution according to farm size as derived from this survey.

	Diseases per farm size				
	Small ($n = 3$)	Medium ($n = 14$)	Large ($n = 12$)	Total	Percentage
IHHNV	0	1	2	3	10.3
White spot	0	4	3	7	24.1
NHP	1	5	6	12	41.3
AHPND	3	8	8	19	65.5
Other vibrios	2	8	5	15	51.7
Parasities	0	1	0	1	3.4

3.2 | Diagnosis

In 54.5% of the reported cases of disease outbreak, the diagnosis is made within the farm by their technical personnel. In the rest (45.5% of the cases), diagnosis is achieved aided by the field inspector assigned by COSAES. When the diagnosis suggests a bacterial disease, only 31.8% of the farms carry out laboratory isolation and sensitivity tests. There is a close correlation of carrying out microbiological identification and antibacterial sensitivity when the attending technician is a Biologist or a technician from COSAES. Aquaculture Engineers or other professionals evade, in most cases, this essential step (14.28%). This latter personnel relies on their so-called "experience" to reach a diagnosis.

Some deficiencies in the procedure in which samples are regularly sent to the Microbiology laboratory were: samples from animals without conspicuous signs of the disease, failure to obtain a sample from the first digestive chamber of the shrimp or gut (target site of *Vibrio*) (Woo et al., 2014); prolonged transfer time from the pond to the diagnosis laboratory, that is, 2–3 h; training in bacterial isolation and identification techniques is required; standardization of antimicrobial susceptibility testing is needed; bacterial susceptibility breakpoints and pharmacokinetic/pharmacodynamic considerations are lacking. Theoretically, these results are contrasted with the quality of the farm's water, as most measure oxygen concentration, salinity, pH, and water translucence twice a day. There is a trained Pathologist available in almost all surveyed farms. He or she carries out macroscopic and microscopic studies and confirms or rules out viral and parasitic diseases based on tissue lesions and findings. Statistical analysis of these procedures also needs to be improved.

3.3 | Use of ABD for disease prevention, control and treatment of diseases

As a compulsory mandate, farms that intend to grow shrimp carry out a microbiological study of the soil. In almost all cases, lime is added to reduce the bacterial load. COSAES' technicians monitor compliance with this procedure. Some farms state that they add probiotics to the water source or include them as an in-feed supplement. Such is the case of Epicin® (Epicore Bionetworks, USA), Sanolife MIC®, Sanolife S® (INVE Aquaculture, USA), PAQ-gro® (Phibro Animal Health Corporation, USA), Shrimp Lyte® (CODEMET, Ecuador), and other brands whose names were not disclosed. Additionally, food supplements such as vitamins and electrolytes are often added.

Regarding the use of antibacterial drugs, there are only six active principles approved for aquaculture in Mexico (SENASICA, 2017), and only 11 pharmaceutical companies manufacture in-feed preparations for shrimp. That is, a total of 37 commercially available products are aimed at treating the different stages of these organisms (Table 4). Although the question was open, and any antibiotic could have been mentioned, the commonest options were oxytetracycline (OXT) 73%, enrofloxacin (ENR) 75%, and florfenicol (FFL) 45%. We failed to discern whether or not

TABLE 4 Authorized antibacterial preparation and other products for aquaculture in Mexico.

Product type	Authorized products
Food	174
Antibiotics and medicated food	37
Food supplements and probiotics	27
Water remediators	22
Vaccines (fish)	2
Dewormers	1
Disinfectants	1
Others (flavors, toxin adsorption aids, sequestrants, antitoxins, etc.)	10
Total	274

Note: Information obtained from the official page of SENASICA. Last visited on 08/31/2022 (https://www.gob.mx/senasica/acciones-y-programas/sanidad-acuicola-y-pesquera).

managers apply a selection criterion to choose a given antimicrobial or brand. Furthermore, the person who reached the final diagnosis was not responsible for acquiring a given product. Only a written petition for an active principle was handed out to the corresponding clerk, often the owner/producer or an acquisitions department. The key criterion for choosing a brand was the price of the product and occasionally a particular recommendation from the representatives of a pharmaceutical company. No pharmacological considerations were put forward to utilize a given antimicrobial drug. That is, withdrawal times, minimal inhibitory concentrations versus hemolymph or hepatopancreas drug concentrations achieved, elimination half-life, possible knowledge of drug distribution, biodegradation of the active principle in ponds and residual water.

The antibacterial drugs are always administered through the oral route as in-feed medication. There are two ways to do so, in the feed plant and manually on the farm. In the former scenario, the farm technician and the pharmaceutical company representative agree on the amount to be incorporated into the feed. The pharmaceutical representative ensures that new food pellets extruded carry the concentration agreed. However, he/she does not share technical data such as pelleting temperature or additives necessary for the extrusion process or whether or not there is information on the loss of the active ingredient in the pelleting process and the lixiviation of the active principle in the ponds. Each food plant has a specific procedure, which is not shared with the producers or technicians. The form of incorporating a given antibacterial drug to feed varies among farms. Some technicians use plain water to dilute/suspend a given drug preparation or even pond water, other farms use vegetable or fish oil as vehicles, some others stir the freshly prepared mixture manually in a large basin, and others do it in a mixer. The resulting combination is painted-smeared onto the feed pellets.

The frequency of antibacterial drugs utilized in the farms is almost identical for either method, 41.3%; 6.9% of the farms use either of the two methods indistinctly, and 10.4% do not use antibacterial drugs. However, doses used show significant variation, ranging from 2 to 25 kg of commercial product per ton of food (Table 5). Likewise, the days on which medicated feed is administered on each farm differ, as there are no clear definition criteria for efficacy and cure. Only one farm offers the treatment once a day, and the others do it every time shrimps are fed, that is, 3.32 ± 0.5 times a day. In this context, Table 7 shows how antibacterial drugs are recommended in the literature.

Regarding the frequency of use, 65.5% of the UPAs surveyed used antibiotics on their farms in the last 2 years; 24.1% have not used antibiotics in the previous 3–5 years, and only 2 UPAs have not used them for more than 6 years. Only 1 UPA reports that they have never administered antibiotics to their organisms. However, these last 3 UPAs acknowledge that they have problems caused by bacteria.

Notwithstanding the above, it is interesting to have learned that the producers rank the use of available antibacterial drugs in their facilities as good or excellent (19/29; 65.5%), and the remaining six UPAs think that they

TABLE 5 Dose of enrofloxacin, oxytetracycline and florfenicol as reported by respondents in shrimp farms in the state of Sonora, Mexico (η = 29).

	Dose				
Farm	Oxytetracycline	Enrofloxacin	Florfenicol	Inclusion method	Minimum withdrawal time enforced (weeks)
1		6 kg/ton		Manual	3
2	5 kg/ton	5 kg/ton	5 kg/ton	Factory[b]	4
3		20 mg/kg of BM	15 mg/kg of BM	Manual	4
4	UI	UI	UI	Both	4
5				NA	NA
6	5 kg/ton	3 kg/ton		Factory	4
7	UI	UI		Factory	2
8		150 mL/sack of food[a]		Manual	6
9		0.4 kg/ton		Factory	6
10	UI	UI	UI	Factory	3
11	5 kg/ton	5 kg/ton	5 kg/ton	Factory	3
12	UI	UI		Manual	2
13	8–12 kg/ton	500 mL/sack of food[a]		Manual	2
14	2 kg/ton	2 kg/ton	2 kg/ton	Manual	2
15	9 kg/ton			Manual	2
16	4 kg/ton	6 kg/ton	UI	Manual	3
17				NA	NA
18		10–20 kg/ton		Manual	2
19	5 kg/ton	5 kg/ton	5 kg/ton	Factory	0
20	5 kg/ton	5 kg/ton	5 kg/ton	Factory	0
21	UI	UI	UI	Both	2
22	UI	UI		Factory	0
23		12–25 kg/ton		Manual	6
24				NA	NA
25	UI	UI	UI	Manual	2
26	3 L/ton[a]		3 L/ton[a]	Manual	6
27	5–10 kg/ton	UI	UI	Factory	2
28	5 kg/ton			Factory	2
29	UI			Factory	4

Note: Empty spaces indicate that the farm does not use that antibiotic.
Abbreviations: BM, biomass; kg/ton, kilograms of product per ton; L/ton, liters of product per ton of feed; ml/sack of food, milliliters of product per bag of 25 kilograms of food; NA, not applicable because this class of antibiotics is not used; UI, undisclosed information.
[a]Disclosed information on the dose used.
[b]Medicated feed from manufacturer.

do it moderately well (6/29; 20.7%). Only one producer thought that their procedures were not right (1/29; 3.4%), and the three remaining producers reported not using antibiotics. The technicians encharged of handling the antibacterial drugs had inadequate training in using these substances. However, 51.7% of them stated that they

TABLE 6 Degree of proficiency, training programs and potential adverse reactions to antimicrobial drugs from surveyed shrimp farms in the state of Sonora, Mexico.

	Farm type			
	Small ($n = 3$)	Medium ($n = 14$)	Large ($n = 12$)	Percentage
Evaluation of proficiency of the operational staff	3	5	7	51.7
Training programs in the use of antimicrobial drugs for the operational staff	3	6	6	51.7
Use of standard operating procedures for the use of antimicrobial drugs	0	3	5	27.6
Claims of a potential adverse reaction to antimicrobial drugs used within the farm	0	0	2	6.9
Use of protective equipment to handle antimicrobial drugs	2	5	8	51.7

possessed the necessary experience and knowledge (15/29), the rest commented that they possessed medium or little knowledge (11/29; 37.9%), and on five occasions, managers mentioned that decision as to whether or not administer an antibacterial drug is taken by the farm owners, is spite of lacking the necessary technical training and ignoring the recommendations of the manager or other professionals. Notably, only 27.6% of the shrimp farms surveyed (8/29) have formalized their operating procedures in writing, and the rest followed verbal instructions. It was detected that protective equipment for operators was available in only 51.7% of the farms (15/29). In contrast, only two farms reported worker problems due to inadequate protective equipment. Affected personnel referred dermatological problems (Table 6).

4 | DISCUSSION

In aquaculture, the use of ABD is widespread, allegedly for treating bacterial diseases (Uddin and Kader, 2006). However, in some countries, it is applied at sub-therapeutic doses as a growth promoter (Liu et al., 2017; Lulijwa, Rupia, and Alfaro, 2020). In Mexico, antimicrobials are formally prohibited as growth promoters, and their use is oriented only as treatment. Notwithstanding, some are still used as performance promoters that is, virginiamycin, which is approved as therapeutic. Nevertheless, there is no study to pinpoint the target organ or tissue and its pharmacokinetic study in shrimp. Antibacterial drugs as growth promoters are also formally prohibited in the European Union since 2006 (EMEA, 2009) and in the United States since 2012 (FDA, 2015), where authorization to use an antibacterial drug must be done by a certified veterinarian. Sadly, it is necessary to recognize the misuse of antibacterial drugs in the treatment of viral diseases. Wrong indications also happen with antiparasitic drugs or the so-called prophylactic substances available to producers without a veterinary prescription, promoting antimicrobial resistance. Such is the case of metronidazole, organophosphates, and malachite green (Shariff et al., 2000). The results of this survey reflect a general ignorance of the proper use of antibiotics, that is, technicians are not clear about what type of pathogens are susceptible to antibiotic treatment, there is almost complete ignorance of the MICs and sensitivity guidance, and they are often used for non-bacterial infections. In Mexico, a certified Veterinarian must issue the prescription for an antibiotic as per NOM-064-ZOO (SAGARPA, 2003). However, deficient surveillance by Mexican sanitary authorities enables producers to have access to almost any antibiotic, generating overuse of these drugs.

In many cases, veterinarians propose antibacterial treatments based on manufacturers' recommended dose or on the recommendation of a specialized pharmacology book in the field of interest. It is assumed that the regulatory authority has already done the necessary review and tests to verify that the antibacterial drugs registered for shrimp are both safe for the species and the environment and effective in treating bacterial disease. However, in shrimp farming, positive results often need to be clarified when using these products. Hence, in addition to the environmental damage, a significant economic load is imposed on this industry.

There is an increasing supply of antimicrobial drugs designed for aquaculture. This is due to the growth of the sector and the ease of obtaining a free sale authorization. Consumers do not ask for pharmacokinetic studies in the target species, validated clinical results, or toxicity. The costs for the use of antimicrobials in shrimp farms in Mexico can vary between 58 and 158 USD per hectare. With an average production of 2.49 Tons per hectare, the maximum final cost per kilogram is 0.063 USD, so it does not represent a significant economic impact and does not affect retail prices. This situation encourages the use of antibiotics. However, the time lost waiting for a favorable response from the administered antibiotic, and the withdrawal time delays the sale of the product derived from a productive cycle and hinders the possibility that the product be exported as consumers worldwide prefer antibiotic-free products, and may exercise their right to reject their purchase due to the potential or real possibility that the product contains pharmaceuticals (Alday-Sanz, 2010).

It is necessary to academically train Veterinarians and Biologists concerning farmed shrimp production, with an emphasis on both diagnosis and treatment of diseases, particularly what this study refers to, the treatment of diseases caused by bacteria. However, training personnel needs to be improved, and much research is still required in this field. Details of the loss of the active ingredient's biological activity during pelleting and feeding medicated feed to shrimp in the ponds are necessary. For example, severe loss of antibacterial activity has been reported for oxytetracycline when medicated food is administered to shrimp in ponds, whether in brackish or sweet water (Laredo et al., 2007).

Furthermore, there is little evidence that its efficacy is explained by its pharmacokinetics and pharmacodynamics (Barron et al., 1990; Martínez-Córdova et al., 2016). For most of the antibacterial drugs used in shrimp farming, the dose, the dosing interval, and the duration of the treatments have not been formally established (George Rigos & Smith, 2015). Thus, in most cases in Mexico, manufacturers have established or proposed the dose of a given antibacterial to treat a bacterial disease. However, the technical and scientific support is limited or lacking.

The success of a given antibiotic therapy depends on many factors. However, one that is essential to rationalize antibacterial treatments is to define the pharmacokinetics of the commercial preparations of the different antibacterial, targeting each of the species of farmed shrimp (Frimodt-møller, 2002; Sumano et al., 2015). These studies must include a pharmacodynamic approach to define if the antibacterial drug reaches the target site and if its antimicrobial activity remains satisfactory within the targeted milieu (Christie & Forsyth, 2008).

Nevertheless, these previous studies are scarce on shrimp, and those available have not been carried out in models that reflect the reality of production in the field. For example, pharmacokinetic studies have been carried out in shrimp *L. vannamei*. However, the antimicrobials were administered through a tube directly placed in the shrimp's first digestive chamber, assuming that these crustaceans ingest the entire dose as a bolus (Fang et al., 2013; Sangrungruang et al., 2004). Alternatively, intrasinusal puncture has been used to deliver the studied antibacterial drug (Chiayvareesajja et al., 2006). In either case, the fact that the medicated food is likely to spend several minutes in the water should not be overlooked. The logical consequence is a loss of antibacterial activity. Undoubtedly, data from these investigations can be rescued, such as relative bioavailability among preparations of a given antibacterial drug. However, they can be considered inapplicable or difficult to correlate with daily production problems (Fang et al., 2013; Ma et al., 2017; Uno et al., 2010).

The use of antibacterial drugs in shrimp farming should be based on scientific evidence and PK/PD ratios (George Rigos & Smith, 2015). In addition, the particular species and culture stage variations should be considered (Toutain et al., 2010), as extrapolation is unwise. For example: for enrofloxacin, the ratios Cmax/MIC90 = 10–12, and AUC/MIC90 = 125, minimize the appearance of resistant mutants and result in optimal and repeatable clinical outcomes. As time-dependant antimicrobial drugs, AUC/MIC90 ratios must be established for florfenicol and oxytetracycline, and a maximum T > MIC90 value should be pursued to optimize their clinical efficacy (Lees et al., 2008). Hence, various pharmacokinetic studies must be carried out, and a microbiological laboratory is required within each UPA. This study revealed that none of the shrimp farms had installed a laboratory for microbiological studies.

TABLE 7 Reported pharmacokinetics of oxytetracycline, florfenicol and enrofloxacin in shrimp.

Species	Route of administration	Dose mg/Kg	Tissue	Cmax μg/mL o μg/g	Tmax (h)	AUC	$T_{1/2}$ (h)	Salinity (1/1000)	T (°C)	F %	Reference
Oxytetracycline											
Atlantic white shrimp *Litopenaeus setiferus*	Intra sinus	10	Plasma	15	0		22.27	20	20	100	(Reed et al., 2004)
		60	Plasma				21.5				
Kuruma shrimp *Panaeus japonicus*	Intra sinus	25	Plasma	28.5	0.5	1102	24.7	22–23	25	100	(Uno, 2004)
	Medicated food with a cannula	50		24.3	10	953	34.3			43.2	
Black tiger shrimp *Penaeus monodon*	Intra sinus	10	Plasma	41.6	0	760	23.1	Sea water	30	100	(Sangrungruang et al., 2004)
	Medicated food with a cannula	10	Plasma	20.2	6	455	6.93			59.9	
Pacific White Shrimp *Litopenaeus Vannamei*	Intra sinus	10	Plasma	32.22	0	266.11	20.74	20	28		(Chiayvareesajja et al., 2006)
			Muscle	7.49	6	166.53	20.9				
			HP	41	9	631.6	14.58				
Pacific White Shrimp Litopenaeus Vannamei	Medicated food with a cannula	50	Plasma	43.52	7	1109	91	20	28	80.62	(Faroongsarng et al., 2007)
			HP	1149	2	12,471	51.3				
Pacific White Shrimp *Litopenaeus Vannamei*	Intra sinus	10	Plasma	40	0	194	11.8	13	27.4	100	(Uno et al., 2010)
	Medicated food with a cannula	10	Plasma	3.37	7	93	14.7			47.9	
		50	Plasma	17.39	10	421.9	11.5			43.6	
Pacific White Shrimp *Litopenaeus Vannamei*	Medicated food (14 days)	132 per day	Muscle	33.54	8 days			36.8	28.6		(Gómez-Jimenez et al., 2008)
			HP	194.37	2 days						
			Plasma	18.79	8 days						
Pacific White Shrimp Litopenaeus Vannamei	Medicated food (14 days)	156 per day	Muscle	33.45[a]	12 days			37.6	29–31		(Bermúdez-Almada et al., 2014)
			HP	223.11[a]	2 days						
Pacific White Shrimp *Litopenaeus Vannamei*	Medicated food	100	Plasma	27.7	6	690	11.01	33	28		(Ma et al., 2019)
			HP	149.42	1	1015	14.89				
			Muscle	0.73	6	31.6	23.53				

TABLE 7 (Continued)

Species	Route of administration	Dose mg/Kg	Tissue	Cmax μg/mL o μg/g	Tmax (h)	AUC	$T_{1/2}$ (h)	Salinity (1/1000)	T (°C)	F %	Reference
Florfenicol											
Black tiger shrimp *Penaeus monodon*	Medicated food	6.6	HP	0.7	1			30	27–28		(Tipmongkolsilp et al., 2006)
			Muscle	0.05	4						
Pacific White Shrimp *Litopenaeus Vannamei*	Medicated food with a cannula THP	10	Plasma	7.96	2	43.7	10.65	Freshwater	25		(Fang et al., 2013)
			HP	204.25	1	1337.74	31.29				
			Muscle	2.98	2	29.1	6.84				
	Medicated food with a cannula FFL	10	Plasma	5.53	2	38.94	17.36				
			HP	164.22	0.5	871.73	41.38				
			Muscle	1.91	2	15.97	18.32				
Oriental prawn *Exopalaemon carinicauda*	IM	10	Plasma	9.44	0.083	69.66	26	27	22		(Feng et al., 2018)
			Muscle	7.34	2						
			HP	14.35	1						
			Gills	5.49	0.5						
	IM	10	Plasma	16.79	0.083	84.72	10.45		28		
			Muscle	10.53	1						
			HP	21.48	0.5						
			Gills	9.6	0.25						
	Medicated food	30	Plasma	4.87	1	39.58	26.76		22		
			Muscle	3.4	4						
			HP	7.06	2						
			Gills	4.51	2						
	Medicated food	30	Plasma	6.99	0.5	69.17	11.39		28		
			Muscle	6.26	2						
			HP	11.68	1						
			Branquias	5.49	1						

(Continues)

TABLE 7 (Continued)

Species	Route of administration	Dose mg/Kg	Tissue	Cmax µg/mL o µg/g	Tmax (h)	AUC	$T_{1/2}$ (h)	Salinity (1/1000)	T (°C)	F %	Reference
Enrofloxacin											
Pacific White Shrimp *Litopenaeus vannamei*	Medicated food	UI	Muscle	0.54 ± 0.26	10 days			36.8	28		(Flores-miranda et al., 2012)[a]
			HP	3.52 ± 1.90	12 days						
			Muscle	0.36 ± 0.17	12 days			36.4	29–31		
			HP	1.60 ± 0.82	10 days						
Pacific White Shrimp *Litopenaeus vannamei*	IM	10	Muscle	5.81 ± 1.46	0.25	90.1	52.3	Freshwater	22–25		(Fang et al., 2017)
			Hemolymph	4.87 ± 1.26	0.083	75.8	19.8				
			HP	11.23 ± 2.31	0.5	274.2	75.8				
Pacific White Shrimp *Litopenaeus vannamei*	Medicated food	30	Hemolymph	19.64	1	299.56	16.07	30	28		(Ma et al., 2018)
			HP	16.29	1	314.47	15.86				
			Muscle	1.95	1	33.99	10.92				

Abbreviations: µg/g, micrograms per gram; µg/mL, micrograms per milliliter; AUC, Area under the curve; Cmax, maximum concentration; FFL, florfenicol; HP, hepatopancreas; IM, intramuscular; mg/Kg, milligrams per kilogram; T, temperature; Tmax, time at which Cmax occurs; THP, thiamphenicol.

[a]UI, In this study, they do not specify the time of sample collection, only the day.

Furthermore, technicians are unaware of how significant it is to determine MIC levels for a given pathogen causing an outbreak.

This survey found that the most commonly prescribed and utilized ABDs in shrimp farms were enrofloxacin, oxytetracycline, and florfenicol. Table 7 presents relevant pharmacokinetics and clinical data in shrimp derived from formal publications. Based on this information, various antibacterial drug preparations were authorized in Mexico for shrimp farming. Even with the above, it is essential to emphasize that pharmacokinetic data presented in these studies offers limited information as drug administration to shrimp was carried out unconventionally to deliver the total dose of the drug to be studied.

In this context, few studies have been conducted to determine these pharmacokinetic parameters from studies under field conditions. An exception was presented by Bermúdez-Almada et al. (Bermúdez-Almada et al., 2014) who measured OXT concentrations in muscle and hepatopancreas during the 10 days, including the 5 days of treatment. The antibacterial drug was included in food pellets. However, the authors only measured drug concentrations once a day, without specifying the time to retrieve each hemolymph sample nor the logic behind this decision. Therefore fundamental pharmacokinetic values such as Cmax, the elimination half-life of the drug, and the T > CMI value cannot be determined.

The administration of antibacterial drugs through shrimp food allows the treatment of a large number of organisms, causing minimum stress. However, if it is done when the disease is affecting food intake, the antibacterial drug dose will decrease (Noga, 2010; Samuelsen & Bergh, 2004). Hence, treatment is often directed to organisms that are not infected yet, that is, as a metaphylactic treatment. If the disease is well-established, treatment efficacy declines sharply.

The chosen antibiotic is incorporated into the pelleted shrimp feed by mixing the active principle with the shrimp feed and then pelleting the mixture. Alternatively, the drug is impregnated onto the existing pellets mixing the active principle with fish or vegetable oil (Duis et al., 1995). Commercial gelatin is used in some cases, depending on the antibacterial drug's water-solubility. In the vast majority of cases, there are no studies on the physiochemical efficiency of these processes, that is, drug release from the preparation, loss of biological activity, and, as already mentioned, the individual pharmacokinetics of each dosage form in each stage of the shrimp's development. There are neither procedure manuals on storing the antibacterial drug preparations nor the impact of the water quality or oils employed for mixing antibacterial preparations with the shrimp's diet when this maneuver is carried out on the farm.

Although the taste capacity of shrimp is not fully characterized, the palatability of the medicated feed has been described as an important factor in treating bacterial diseases in this species. Some studies have verified the rejection of high doses of some drugs (Rigos, Alexis, & Nengas, 1999; Stoffregen, Backman, Perham, Bowser, & Babish, 1996). The unpleasant-bitter taste of most antibacterial drugs is known to be a negative factor in achieving a correct dosage when incorporating the active principle into the shrimp feed (Doi & Stoskopf, 2000). Some producers attribute the refusal of medicated food to the excipients utilized. This view has prompted some producers to try to obtain pure active principles and manufacture their own medicated feed, even though the local regulations prohibit it (NOM-040-ZOO-1995). Punitive legal measures must be established to inhibit this conduct, as it entails an obvious danger to workers, Public Health, or both and is likely to induce overdosing or underdosing (Shariff et al., 2000).[3]

Lixiviation is understood as the separation of the soluble from insoluble fractions of an antibacterial drug when dissolved in the water pond. Xu and Rogers (Xu & Rogers, 1994) mention that the losses of oxytetracycline by lixiviation when included in pellets depend on the temperature, the pH of the pond's water, the vehicles included, and the size of the pellet. Consequently, each commercial preparation of oxytetracycline must carry out its lixiviation tests and present the information to consumers. Such information may be used when shrimp producers buy food and request that the active principle is included. Particular orders are usually made, and they amount several tons of food in specialized factories. The pharmaceutical and food industry response may require weeks, so pharmaceutical

[3]NOM 040 ZOO 1995: *Especificaciones para la comercialización de sales puras antimicrobianas para uso en animales o consumo por éstos*. From: http://publico.senasica.gob.mx/?doc=516. Last consulted on April 14 2022

stability studies in different diets must also be added. Duis et al. (1995) studied drug-decay with trimethoprim/sulfamethoxazole, oxolinic acid, oxytetracycline, and amoxicillin. The drugs were added to a pelleted feed using a mixture of oil and the chosen drug. Samples were analyzed various times, and results revealed that some antibacterial drugs decay of up to 8.8% in just 30 s and up to 67% in 15 min. This study shows the complexity of treating shrimp with antibacterial drugs as the feeding behavior and physiology of the gastrointestinal apparatus in shrimp only allow the intake of their food slowly. This explains, in part, why antibacterial treatments often fail in this species.

Another problem to solve when treating shrimp affected by a bacterial infection is the calculation of the biomass in each pond. This is important as collected data modifies the perception of the success or failure of a given treatment. The amount of drug to be administered can again be over or under-calculated, and the amount of survival to a given pathogenic event would be difficult to assess. This study found that biomass is determined through various procedures, mainly the so-called population method, secondarily by the feed consumption method, and occasionally by a combination of both. It is worth noting that the accuracy of the data obtained with these methods depends on the operator's skill, the tank's depth, the weight of the network's weights, wind speed, time of day, the state of shrimps' molting, and the lunar cycle.

Based on the lack of data described, it is not surprising that the dose used in each farm may vary greatly, as far as concentration added to the feed is concerned, and based on the dosing intervals elected. Hence, more reliable technical support is needed to know the pharmacokinetics of the active principle in shrimp for each pharmaceutical preparation. In turn, all these factors make elusive the certainty of efficacy. Data gathered from this study allow the proposal that it is necessary to review the supporting documentation of the available commercial preparations of antibacterial drugs to treat shrimp.

In addition, pharmaceutical companies, regulatory authorities, and Universities can create research strategies to obtain the necessary data and guarantee the optimal use of antibacterial drugs in shrimp farming. Likewise, a constant training program for the personnel in charge of antibacterial treatments, both in terms of the rational use of these drugs and biosafety to handle such preparations, must be completed on time. It is also worth noting that there are no Veterinary Doctors in charge of antibacterial treatments in the UPAs of the State of Sonora. Nevertheless, veterinary products are the ones used in shrimp farming. Almost all technicians interviewed know that a severe problem of bacterial resistance is growing worldwide (Holmström et al., 2003; Li et al., 2016; Liu et al., 2017; Mo et al., 2017; Moreau & Neis, 2009; Rico & Van den Brink, 2014; Tipmongkolsilp et al., 2006), and that virtually all human or veterinary activities should be reexamined to minimize the future impact of antibiotic resistance.

5 | CONCLUSIONS

This field survey on the use of antibacterial drugs in shrimp farming in the State of Sonora, Mexico, reveals that essential improvements are needed to achieve certainty in the diagnosis of the diseases occurring in this area and consequently in setting a responsible use of these drugs. Ongoing training programs in the pharmacology of aquatic animals could minimize the incorrect use of antibacterial drugs. Specific pharmacokinetic studies of antibacterial drugs used in the field are urgently needed to rationalize their use. Calculation of biomass, the quality of water, the ingredients of the food, the form of incorporation of the drug, the feeding behavior of the species, and other considerations must support each pharmacokinetic study and focus on measuring the drug concentration in the target tissue should follow. Additionally, the pharmacokinetics of antibacterial drugs must be carried out in healthy and disease-affected shrimp to determine differences in drug bioavailability, drug distribution, half-life, Cmax, and kinetics of residue elimination. The gathered information can contribute to defining drug claims and improve the safety of the different preparations to treat bacterial diseases in shrimp.

This survey was not designed to uncover risks associated with consuming shrimp cultured in farms from the State of Sonora. However, it is not possible or ethical to disregard the fact that sanitary and regulatory agencies in Mexico exercise minimum or no control over the use of ABDs. There is no program to help reduce their use or promote their better use and observe adequate withdrawal times. Therefore, it is possible that shrimp products contaminated with ABDs could reach consumers' tables. From an academic field, it is proposed that Mexico's sanitary and regulatory authorities carry out sampling in the local national markets and in export shrimp to define the reality of drug residues in this species and that traceability programs be structured.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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