Review

A One Health Perspective to Recognize *Fusarium* and *Neocosmospora* as Important in Clinical Practice

Valeri Sáenz [1], Carlos Alvarez-Moreno[2], Patrice Le Pape[3], Silvia Restrepo[4], Josep Guarro[5], Adriana Marcela Celis Ramírez [1]*

[1]Grupo de Investigación Celular y Molecular de Microorganismos Patógenos (CeMoP) Departamento de Ciencias Biológicas, Universidad de Los Andes, Bogotá, Colombia; v.saenzm@uniandes.edu.co
[2]Universidad Nacional de Colombia, Bogotá, Colombia; caalvarezmo@unal.edu.co
[3]Département de Parasitologie et Mycologie médicale, EA1155, IICiMed, Université de Nantes, Nantes, France; Patrice.Le-Pape@univ-nantes.fr
[4]Laboratorio de Micología y Fitopatología (LAMFU), Facultad de Ingeniería, Universidad de Los Andes, Bogotá, Colombia; srestrep@uniandes.edu.co
[5]Facultat de Medicina I Ciéncies de la Salut, Departament de Ciéncies Médiques Básiques, Unitat Microbiología Universitat de Rovira I Virgili, Reus, España.
* Correspondence: e-mail: acelis@uniandes.edu.co, ORCID: 0000-0003-3057-1966 Universidad de Los Andes, Carrera 1A # 18A -12, Bogotá, Colombia. Tel: +57 1 3394949 ext. 3757.

Abstract: A strategy to propose solutions to health-related problems recognizes that people, animals, and the environment are interconnected. *Fusarium* and *Neocosmospora* are an example of this interaction due to the capable of infecting plants, animals, and human. This review provides information on various aspects of these relations and proposes how to approach fusariosis with a One Health methodology. Here we give a framework to understand infection pathogenesis, through the epidemiological triad and explain how the broad utilization of fungicides in agriculture may play a role in the treatment of human fusariosis. We assess how plumbing systems and hospital environments might play a role as a reservoir for animal and human infections. We explain the role of antifungal resistance mechanism in both humans and agriculture. Our review emphasizes the importance of developing interdisciplinarity research studies where aquatic animals, plants, and human disease interactions can be explored through coordination and collaborative actions.

Keywords: *Fusarium*, *Neocosmospora*, One Health

1. Introduction

The One Health concept is defined as a worldwide strategy for expanding interdisciplinary collaborations and communications in all aspects of health care for humans, animals and the environment [1]. *Fusarium* and *Neocosmospora* have been described as pathogens of humans, animals, and plants a phenomenon known as trans-kingdom pathogenicity [2,3]. In recent years, human infections by *Fusarium* and *Neocosmospora* are rising worldwide mostly involving immunocompromised hosts [3,4]. To understand these human infections, we must explore the dynamics among the host (human/animal), the pathogen and the environment.

In humans, these fungi cause a broad spectrum of infections, including both superficial (onychomycosis and keratitis), and disseminated diseases (particularly in hematological cancer and neutropenic patients) [5]. Fungal keratitis is a very common cause of corneal infection in developing countries and recognized as a significant cause of ocular morbidity and blindness [6,7]. The goal of this revision is to provide an assessment of the current conceptions in one health approach and host-pathogen interaction which help clinicians to consider *Fusarium* and *Neocosmospora* as important human pathogen.

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2. Fusaria species

The taxonomy of the genus *Fusarium*, initially described by Link in 1809 as presenting banana shape conidia, has been changing in taxonomy over the years and it has become a controversial issue [8]. Currently, the genus *Fusarium* has been classified into species complexes, i.e *F. solani* species complex (FSSC), *F. oxysporum* species complex (FOSC), *Gibberella* (Fusarium) *fujikuroi* species complex (GFSC), *F. incarnatum* - *F. equiseti* species complex (FIESC), *F. sambucinum* species complex (FSAMSC), *F. tricinctum* species complex (FTSC), *F. chlamydosporum* species complex (FCSC) and *F. dimerum* species complex (FDSC) [9–11]. In addition, the members of FSDC have been included in the genus *Bisifusarium* [12] and recently, it has been proposed that members of the *F. solani* species complex to be moved to the genus *Neocosmospora* based on the results of phylogenetic analysis [13]. This includes the species *N. petroliphila* (*F. petroliphilum*), *N. keratoplastica* (*F. keratoplasticum*), *N. falciformis* (*F. falciforme*) and *N. solani* (*F. solani*), along with the new species *N. gamsii* (haplotype 7), *N. suttoniana* (haplotype 20) and *N. catenata* (haplotype 43) [14]. However, a recent phylogenomic analysis supports FSSC as *Fusarium* (Geiser 2020 paper under review) and the genus name *Fusarium* for human pathogens in the FSSC (ODonnel 2020 article in press). Taking into account that the continuous change of names of these fungi can create some confusion it has been suggested to refer to these taxa as *Fusarium*-like [15].

3. *Fusarium* and *Neocosmospora* in agriculture

Fusarium species are broadly distributed in soil and on underground and aerial plant parts, plant debris, natural substrates [8], and furthermore found in aquatic habitants, including natural water environments and air [16,17]. For instance, FSSC is a varied group of fungi capable of causing diseases on a wide variety of plants. It is considered the fifth plant pathogen in the list of "top ten fungal plant pathogens" [18]. On the other hand, *Fusarium* wither can influence and injury ornamental plants at all production stages. *Fusarium oxysporum* f. sp. *dianthi* and its sister species, *F. redolens* f. sp. *dianthi*, keep on causing serious losses at any place where carnations are grown and remains agents of critical disease for this crop [19]. These pathogens additionally attack cereals that are significant for human and animal nutrition. It explicitly infects certain parts of the plants, for example, grains, seedlings, heads, roots or stem, causing various diseases, reducing product quality and diminishing business yield. Some species produce important mycotoxins, such as fumonisin, deoxynivalenol, and zearalenone [20].

Therefore, managing *Fusarium* outbreaks is a significant issue in agriculture. Efforts made to decrease agricultural losses by the fungal disease incorporate chemical, biological control, and fungicide use, particularly azoles compounds [21,22]. The present use rates for some triazoles, which are the biggest class of azole fungicide , are around 100 g/ha of culture [22]. The substantial utilization of azoles in agriculture is currently a major worry in clinical practice since it could induce antifungal resistance among diverse human fungal pathogens. Indeed, previous studies have informed the presence of environmental resistance to azoles of medical importance in *Aspergillus fumigatus* isolated from flower fields related to the use of azole fungicides [23–26]. This resistance has also been reported in other environmental sources such as compost sites, public/private gardens, vineyard and agriculture soil [27,28]. In India, a study from environmental sources including soil, plants, gardens parks and agricultural fields reported *F. falciforme* and *F. keratoplasticum* with high Minimum inhibitory concentration (MIC) values to fluconazole, ketoconazole and terbinafine [29]. Colombia being the second flower exporters in the world, including carnation which is commonly affected by some species of *Fusarium* could remain a country of concern. About 6,800 hectares, 75% of which are located in the savannah of Bogotá are destined for the cultivation of flowers for export [30]. Based on the Colombian Agricultural Institute report, fungicides acting by inhibition of ergosterol synthesis are approved to use in the flower activity [23,31]. This data underlines the need to study *Fusarium* and *Neocosmospora* in crops, flower fields, and clinical settings.

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3.1. *Fusarium* and *Neocosmospora* *in* hospital environment

Water distribution systems (drains, faucet aerators, shower heads) in hospitals have been identified as potential reservoirs for species of *Fusarium* and *Neocosmospora*, where they are thought to be responsible for nosocomial infections [32]. Most of the pathogenic species of these fungi have been found in environmental samples, including plumbing systems of hospitals [33]. During hospital outbreaks affecting immunosuppressed hosts, genotyping approach has shown a relationship between hospital water and patient isolates. This suggest that shower is most likely the mechanism of aeral dispersal of the conidia in air and could be responsible for the transmission to the host [32,34]. Furthermore, airborne conidia may also represent a relevant source of infection as occurred in the case of poorly sealed chase openings permitting inadequate air exchange and exhausts [35]. A recent study informed a genetic relationship between *Fusarium* species isolated from indoor hospital air with the ones recovered in blood cultures of hematologic patients, suggesting that the air may be a potential source for fusariosis [4]. Airborne fusariosis is considered to be acquired by the inhalation of airborne *Fusari*um conidia, as suggested by the occurrence of sinusitis and or pneumonia in the absence of dissemination [36].

4. *Fusarium* and *Neocosmospora* animal disease

Fusaria-like fungi are important cause of opportunistic infection in aquatic animals, such as seahorses, turtles, dolphins and pinnipeds and colonization of eggs. *Fusarium* infection is considered as the primary driver of declining turtle populations around the world [37]. The sea turtle egg fusariosis (STEF) is a recently emerging disease and is responsible for egg mortality in sea turtles around the world; most of the cases related to *N. keratoplast*ica and *N. falciformis* [38–43]. It has been demonstrated that during the embryonic development, the eggs spend an extensive time-stretch secured by sand under states of high stickiness and a warm and consistent temperature; it has been suggested that these conditions support the development of soil-borne fungi such as *Fusarium* [39,43]. Clinical manifestations that suggest possibly STEF include the presence of atypically colored areas (e.g., yellow, blue, gray, red) on the eggshell, with more severe infections showing gray hyphal mats on the outside and the inside of the eggs and on the embryos [43]. The clinical signs of infection caused by *Fusarium* in aquatic animals shift from a superficial invasion of the skin to pulmonary or systemic infections affecting the lungs, liver, heart, and cartilages [37].

Some of the principal hypotheses on the STEF etiology and epidemiology lie in the relationship between beach environment and human environmental sources. *N. keratoplastica* and *N. falciformis* are probably microbiota of beach sand, and there is a relationship between human construction plumbing systems and STEF disease. These pathogens brought into the sand beach by overflow from plumbing human contaminations [39].

Other cases related to animal pathologies are equine keratitis infections [44] and invasive sinusitis and facial mycetoma in dogs [45]. In addition, it has been accounted raised concentrations of fumonisins in animals feed cause sicknesses, as Equine Leukoencephalomalacia (ELEM) in horses and porcine pulmonary edema (PPE) or liver injury in pigs [20].

5. *Fusarium* and *Neocosmospora* in human diseases

Fusariosis is, after aspergillosis, the second most common mold infection in humans [9]. These fungi cause superficial, such as onychomycosis and keratitis, locally invasive, and disseminated disease.

5.1 Onychomycosis

Onychomycosis is one of the most widely recognized nail infection with an overall prevalence of 5.5% [46]. This pathology can affect the physical, functional, psychosocial and emotional aspects of life

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[47]. Even though it is not a life-threatening condition, numerous significant anatomic nail functional purposes may be affected, such as difficulty in walking, emotional embarrassment and, work- related challenges are the most commonly reported issues. [47]. Recognized risk factors for onychomycosis are trauma, increasing age, obesity, diabetes, participation in fitness activities, immunosuppression (HIV, drug-induced), malignancies and occlusive footwear [46–48]. People who have pedicure treatment are less likely to acquire onychomycosis [49].

Dermatophytes, mainly *Trichophyton rubrum*, are responsible for most fungal nail infections and about 30% to 40% of onychomycosis cases are caused by nondermatophyte molds (NDMs) and yeasts [46]. The most common NDMs organisms are *Scopulariopsis brevicaulis*, *Aspergillus* spp., *Acremonium*, *Fusarium* spp., *Alternaria alternata*, and *Neoscytalidium*. In South America, studies suggest that fusarium-like fungi may be the most common NDMs. [49,50]. Species identification has a crucial role in this disease, for example, *N. keratoplastica* and *N. falciformis* are the most frequent species isolated in Colombia, and some of these isolates exhibited lower azole -*in vitro* activity [49].

Regarding pathogenesis, onychomycosis is acquired through direct contact of the nails with *Fusarium in* the environment [46]. Fungal production of proteases that degrade keratin may facilitate invasion [51]. In addition, histological investigations have demonstrated the capacity of *F. oxysporum* to invade human nails, including the firm attachment to the nail plate and the dissemination to deep layers causing disorganization of nail structure [52]. Also, the formation of fungal biofilms is a contributor to persistent infection, which offers advantages such as antifungal resistance, protection against host defenses, increased virulence, communication, metabolism cooperation and differential community based gene expression [52–54]. A scanning electron microscopy (SEM) showed that this fungus is able to form a biofilm, penetrating unassisted nail layers to cause onychomycosis and that the ventral surface of the human nail is more vulnerable to infection than the dorsal surface [52].

5.2 Keratitis

Corneal disease is one of the leading causes of blindness worldwide. In 2001 it was reported that trauma and corneal ulceration are essential causes of unilateral blindness and that the global estimate varies from 1.5 to 2 million cases per year [6]. Current epidemiological information proposes that microbial keratitis might be epidemic in South, South-East, and East Asia and may exceed 2 million cases per year worldwide [55]. It has furthermore been shown that fungal contrasted to bacterial keratitis can be progressively destructive. One, retrospective analyses found fungal keratitis was more likely to perforate the cornea than bacterial keratitis (OR=5.86, 95 % CI, 1.35–20.66) and lead to irreversible change[56]. Likewise, around 15-27% of patients with fungal keratitis require surgical intervention such as corneal transplantation, removal of ocular contents and, enucleation as a result of the failure of pharmacological treatment [57].

The requirement for prolonged and intensive treatment, the ocular outcomes (loss of vision and / or loss of the eyeball), indicate that the economic and medical implications are high [58]. In addition, a correlation between gross national income (GNI) and the etiology of microbial keratitis has been determined. Fungal keratitis is associated with countries with low GNI [59]. Furthermore, there is an extent of cases of fungal keratitis related to the utilization of contact lenses. Between 2004 and 2006, an outbreak of *Fusarium* fungal keratitis occurred in contact lens users worldwide, due to the loss of the disinfection capacity of a contact lens solution [60]. Clinical signs of fungal keratitis consist in sudden onset of pain along with photophobia, discharge with a reduced vision and opacity on the surface of the cornea [61].

The common fungal causative agents are *Fusarium* spp., *Aspergillus flavus* and *A. fumigatus* and *Candida albicans* (less common in tropical climates) [62]. *Fusarium* keratitis has increased over the most recent forty years and it is estimated that around half of all the cases of microbial keratitis in tropical countries, is caused by this genus. It is probably due to an increase in the use of topical steroids and

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antibacterial agents, as well as an increase in surgical procedures, contact lens use, ocular trauma, chronic ocular surface diseases, and immune compromised patient [63]. In Tunisia, fungal keratitis represents 83% of the cases, being *F. solani* the most prevalent species (66%)[64]. In Brazil 25% of fungal keratitis are caused by *Fusarium* [65] and in Mexico *F. solani* was found in 37% of patients [66]. Recent studies done in South India have informed that among *N. falciformis* and *N. keratoplastica* were the most prevalent species isolated from both human keratomycoses and environmental settings [29].

The interaction of pathogenic fungi with host cells is the main factor in the pathogenesis of mycotic keratitis. The human central corneal temperature (32.6 ± 0.70 °C), is appropriate for the development of *Fusarium* [67]. Adherence of microorganisms to host cells through an assortment of adhesins is essential for the initiation of the infection [61]. Consequently, *Fusarium* keratitis can invade the cornea and the anterior chamber of the eye. There, in the pupillary area, it forms a lens-iris-fungal mass which affects the normal drainage of the aqueous humor and causes an increase in the intraocular pressure producing fungal malignant glaucoma [61,68]. Also, *Fusarium* mycotoxins can suppress immunity and break down tissues. Certain cytosolic proteins and peptide toxins can destroy corneal epithelial cells [69]. Proteases play an important role in fungal keratitis because they can cause corneal ulcer [61,70]. The PacC/Rim 101 transcription factor of *F. oxysposrum* may be involved in the survival and growth on the ocular surface [71]. As described in onychomycosis, the formation of biofilm is another factor that contributes to the pathogenesis of keratitis as well to antifungal resistance [72,73]. Biofilm proteomics studies in *N. falciformis*, have identified several proteins whose levels changed during the biofilm formation phases, as well as the enzymes involved in the glycolysis / gluconeogenesis and pentose pathways. Some of the proteins involved could promote angiogenesis, adhesion / invasion and immunomodulation [73].

5.3 Invasive disease

Invasive fusariosis affects most patients with prolonged and profound neutropenia and/or severe T-cell immunodeficiency, acute leukemia and hematopoietic cell transplant (HCT) recipients and is the most frequent and is the most common challenging clinical form of fusariosis in immunocompromised patients, accounting for approximately 70% of all cases of fusariosis in this population [36]. A retrospective analysis of 233 cases (92% of which involved patients with hematologic diseases) reported that the outcome is usually poor, with a 90-day probability of survival of 43% [74].

The typical clinical onset is that of a patient with prolonged (>10 days) and profound (<100 cells/mm^3) neutropenia who is persistently febrile and develops disseminated and characteristic skin lesions (erythematous papular or nodular lesions), with a positive blood culture [36,75]. *Fusarium solani* is the most common species involved in fusariosis (50% of cases), followed by *F. oxysporum* (20%) and *F. verticillioidis* and *F. moniliforme* (10% each) [4].

Animal models of fusariosis showed mortality was correlated with inoculum size [36]. In nonneutropenic mice the disease was described by necrotizing abscesses with hyphae, hemorrhage, and neutrophil and macrophage infiltration [76]. Paradoxically, neutropenic mice did not exhibit an inflammatory cellular reaction and had a significantly higher fungal burden [76]. A murine model of intratracheal inoculation of *F. solani* was recently used to investigate its spread to different organs in immunocompetent animals within 24 h after inoculation, results showed that a 1x10^8 conidia / animal inoculum results in 100% death of immunocompetent mice in 24 hours [77].

6. Fungicides, antifungals and human fusariosis treatment

Before reviewing human fusariosis treatment, we must discuss a frequently forgotten issue in clinical practice: the role of the environment and fungicides in the patient response to antifungals drugs.

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Fungicides are chemical agents utilized for control and treatment of fungal infections in plants. They exhibit a variety of mechanisms of action, such as effects on respiration, signal transduction, mitosis cell division, membrane and cell wall [78]. Azole fungicides which include tebuconazole, propiconazole, epoxiconazole also called demethylation inhibitor (DMI) are the most widespread treatment in agriculture due to their low cost and broad-spectrum [79]. For example, tebuconazole is generally used to control FHB (*Fusarium* head blight) [80]. Tebuconazole demonstrated various effects on *Fusarium culmorum* (a common pathogen of cereals), including morphological changes at the ultrastructural level such as considerable thickening of the hyphal cell walls, excessive septation, the formation of the incomplete septa, extensive vacuolization, accumulation of lipid bodies and progressing necrosis or degeneration of the hyphal cytoplasm [81]. Besides, *F. culmorum* is capable of adapting to triazole pressure by overexpressing a drug resistance transporter [82].

As referenced before, the overuse of fungicides in crops and flower fields becomes imperative for the identification of *Fusarium* and *Neocosmopora* to species level (some species have higher MIC values than others) and not only from an epidemiological viewpoint but also for choosing the appropriate antifungal treatment [83].

6.1 Localized infection

There are currently no available antifungal recommendations in accordance with *Fusarium* isolation. Despite treatment with nail lacquers and systemic treatment is usually used, *Fusarium* onychomycosis and keratitis are difficult to eradicate. In the case of onychomycosis systemic treatment with itraconazole or terbinafine is usually effective, but relapses are very common [84]. Some *Fusarium* strains isolated from nail sample have also demonstrated *in vitro* susceptible to amphotericin B [49]. Additionally, treating fungal keratitis is challenging because of the limited and variable susceptibility of *Fusarium* and *Neocosmospora* to antifungal agents, the poor tissue penetration of topical antifungal agents resulting in low drug bioavailability and the absence of routine determination of antifungal susceptibility [85]. First-line therapy for fusaria keratitis includes a topical antifungal agent either alone or in combination with systemic antifungal medication. Natamycin has been the traditional drug of choice for topical treatment, although amphotericin B drops (1.5 mg/mL) and voriconazole have also been used [86]. Other, randomized trial comparing topical 5% natamycin with topical voriconazole 1% for the treatment of fungal keratitis (24.6% of which were caused by *Fusarium*), suggested that natamycin may be more effective in healing corneal ulcers and improving visual acuity [87].

6.2 Invasive infection

There is a variable susceptibility of *Fusarium* spp. to antifungal agents. The empiric treatment for invasive fusariosis infections is either voriconazole (VRC) or liposomal amphotericin B (L-AMB), surgical debridement (if conceivable), and posaconazole for salvage therapy [88]. If conceivable, neutropenia recovery and surgical debridement could be elements of the management. Information displays a 90-day survival of 42% in patients treated with voriconazole and showed that combined therapy is no better than voriconazole alone [89]. In patients with acute leukemia L-AMB or VCR is preferred. The ending point of invasive infection highly depends on persistent neutropenia and or corticosteroid-induced immunosuppression [90]. *In vitro* synergism between antifungals and antimicrobials or nonantifungal agents have been demonstrated; percentages of synergism was of 80% for amiodarone (AMD) + VRC, of 75% for moxifloxacin and AMB and of 65% for AMD + AMB of 65% [91].

7. Antifungal resistance mechanisms

In general the members of *Fusarium/Neocosmospora* have showed primary or secondary resistance to practically all currently used antifungals such as azoles, echinocandins, and polyenes [92]. An

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organism that is resistant to a drug prior to exposure is described as having primary or intrinsic resistance. Secondary resistance develops in response to exposure to an antimicrobial agent [93]. Both of these mechanisms have been reported in these fungi, although the molecular mechanisms of intrinsic resistance have not been described yet in them [11]. Secondary resistance to azoles has been demonstrated in *A. fumigatus*, and is usually dependent on altered expression of *CYP51*, the gene encoding sterol 14α-demethylase [94,95]. In the genus *Fusarium*, three paralogous *CYP51* genes have been depicted and assigned as *CYP51A*, *CYP51B*, and *CYP51C*. In agriculture samples, the overexpression of *CYP51A* in *F. graminearum* in the presence of tebuconazole has already been described [96]. More recent evidence shows that *N. keratoplastica CYP51A* mRNA levels are ~6,500-fold upregulated in response to azole antifungals to compensate for the loss of *CYP51B* function due to azole inhibition. A strong association of voriconazole resistance with a 23 bp CYP51A promoter deletion in *N. keratoplastica* isolates was also demonstrated [97].

Furthermore, recently was reported for *F. oxysporum* and *N. solani* that several genes related to mechanism of antifungal resistance such as ergosterol synthesis pathways, drug efflux pumps, response to oxidative stress, and cell wall biosynthesis, related to mechanisms of antifungal resistance were differentially regulated upon the treatment with amphotericin B (AMB) and posaconazole (PSC) [98].

8. One Health perspective

The emphasis of One Health approach may explain common points such as STEF disease and plumbing human contaminations, hospital water and air distribution systems as reservoir, risk of human infection from environmental source, for example fusaria keratitis may develop following the traumatic inoculation of *Fusarium*/*Neocosmospora*-contaminated soil or plant material (Figure 1).

Furthermore, the extensive use of azoles fungicides in agriculture leading to a risk of antifungal resistance in humans is a significant issue of concern. Azole fungicides utilized in agriculture share the same mechanism of action (inhibition of lanosterol-14α-demethylase) and similar molecular structures (pharmcophores) as medical triazole drugs [99]. Furthermore, a recent rate of emergence of fungicide-resistance pathogens has been informed [100]. Overall, all these findings challenge clinicians and researchers to understand all the parts of the puzzle. We must continue efforts to think outside the box, work together with all actors of one health initiatives, integrate fungal diseases into health systems[101] and improve interdisciplinarity studies that include the patient, the environment and the relationship among all the elements that affect fusariosis in agriculture, human and animal diseases.

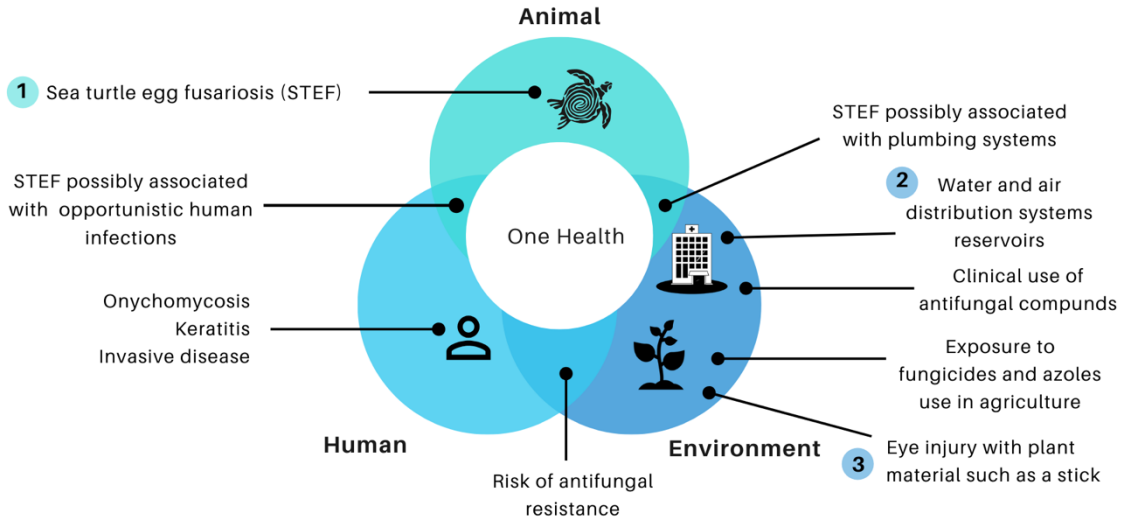

Figure 1. Animal, Environment and human interaction a One Health perspective.

9. Conclusions

Fusarium and *Neocosmospora* share the ecosystem, they live in. Data from fusariosis infection in animals and plants are vital to understand the human infections. Fungicide controls fungal disease but many fungicides share target activity with antifungals explaining that the high use of fungicides in agriculture is a risk for developing resistance to antifungals in clinical practice. To adequately recognize fusariosis disease in humans, animals and plants, epidemiological information, and research should be done across all segments. Government, agriculture, clinical, veterinarian, and plant authorities must joint actions to respond to One Health approach in fusariosis.

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