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Review

A Comprehensive Review of Common Bacterial, Parasitic and Viral Zoonoses at the Human-Animal Interface in Egypt

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Abstract: Egypt has a unique geographical location connecting the three old-world continents Africa, Asia and Europe. It is the country with the highest population density in the Middle East, Northern Africa and the Mediterranean basin. This review summarizes the prevalence, reservoirs, sources of human infection and control regimes of common bacterial, parasitic and viral zoonoses in animals and humans in Egypt. There is a gap of knowledge conerning the epidemiology of zoonotic diseases at the human-animal interface in different localities in Egypt. Some zoonotic agents are "exotic" for Egypt (e.g., MERS-CoV and Crimean-Congo hemorrhagic fever virus), others are endemic (e.g., Brucellosis, Schistosomiasis and Avian influenza). Transboundary transmission of emerging pathogens from and to Egypt occurred via different routes, mainly importation/exportation of apparently healthy animals or migratory birds. Control of the infectious agents and multidrug resistant bacteria in the veterinary sector is on the frontline for infection control in humans. The implementation of control programs significantly decreased the prevalence of some zoonoses, such as schistosomiasis and fascioliasis, in some localities within the country. Sustainable awareness, education and training targeting groups at high risk (veterinarians, farmers, abattoir workers, nurses, etc.) are important to lessen the burden of zoonotic diseases among Egyptians. There is an urgent need for collaborative surveillance and intervention plans for the control of these diseases in Egypt.

Keywords: zoonotic diseases; Egypt; influenza; MERS-CoV; rabies; cryptosporidiosis; fascioliasis; campylobacteriosis; salmonellosis; Middle East

1. Introduction

Zoonotic diseases (ZD) are those infections that can be naturally transmitted from animals to humans with or without vector [1]. In the past few decades, there has been a rise in the outbreaks of zoonotic diseases which have an enormous socioeconomic impact worldwide, for instance, all foodborne zoonoses occured in a single country costs about $1.3 billion annually [2]. Additionally, ZD constitute 61% of all communicable diseases causing illness in humans and about 75% of emerging human pathogens [3–5]. More than 75% of the diseases that affected humans have been transmitted from animals or animal products [1]. Zoonotic diseases can be transferred from animals to humans by several ways such as the consumption of contaminated food and water (e.g., cryptosporidiosis), exposure to the pathogen during processing (e.g., campylobacteriosis and salmonellosis), direct contact with infected animals (e.g., avian influenza) and by pets scratches or bite (e.g., rabies) [6–10]. Some emerging zoonoses expanded their host range and their incidence increased (e.g., avian influenza). This expansion occurred as a result of global trade, increase poultry production, climate changes, bird migration, human movement, and the burgeoning global population. Several animal reservoirs of ZD have been identified, including ruminants, equines, poultry, rodents, dogs and cats, mosquitoes and ticks, which were considered a potential risk of disease transmission [11–14]. Furthermore, antimicrobial resistance considered as an additional risk associated with exposure to zoonotic pathogens because it is potentially limits disease treatment options in both public health and veterinary settings [14]. Therefore, prevention and control programs should be implemented by public health and veterinary officers to combat the sources and reservoirs of zoonoses especially after the development of antimicrobial resistance problem due to misuse of antibiotics [12].

Egypt is located in the north-eastern part of Africa connecting the three old-world continents Africa, Asia and Europe. It is the county with the highest population density in the Middle East, North Africa and the Mediterranean basin with about 90 million inhabitants. Egypt has 27 governorates and over 90% of the population live in 10% of the whole area along the River Nile and Nile Delta in the northern part of the country. A number of zoonotic pathogens have been reported in Egypt. The burden of ZD is provoked by factors such as the method of control, environmental factors, behavioral factors, social factors, clinical manifestations, the socioeconomic impact of such diseases and mode of transmission. The highest incidence and prevalence of zoonotic diseases in Egypt may be attributed to the deficiency of suitable control mechanisms, inadequate infrastructure and lack of information on their significance and distribution. However, there is a marked decrease in the prevalence of some ZD (e.g., schistosomiasis). In this review, we will focus on the most important and prevalent emerging and re-emerging ZD in Egypt including the current situation, reservoirs, sources of human infection and control regimes, if available.

2. Bacterial Zoonosis

2.1. Campylobacteriosis

Campylobacteriosis is a zoonotic disease which has a worldwide public health impact and is caused mostly by *Campylobacter jejuni* or *Campylobacter coli* [15]. *Campylobacter* is S-shaped, or curved rod-shaped bacteria of the epsilon class of Proteobacteria [16]. Poultry are a natural reservoir and are frequently colonized with thermophilic *Campylobacter* species, primarily *C. jejuni* and *C. coli*. Although *Campylobacter* is insignificant for poultry health, it is a leading cause of foodborne gastroenteritis in humans worldwide. Contaminated poultry carcasses are recognized as the main source for human exposure [17]. It is extremely difficult to keep poultry flocks free of *Campylobacter* which is commonly present in the poultry houses environment. During the slaughtering process, contamination of the carcasses with high numbers of *Campylobacter* is unavoidable [18].

The disease is endemic in Egypt and is a major cause for pediatric diarrhea. Nonetheless, the epidemiology in animals and humans has not been fully characterized. In the period from 2006 to 2015, several studies described the isolation of *Campylobacter*, mainly *C. jejuni*, in chickens, raw milk, milk products, diarrheic and normal camel calves and stool of diarrheic patients in several governorates in Egypt [19–23]. Backyard poultry remains the main source of *Campylobacter* transmission to humans [24–26]. In one governorate, *Campylobacter* spp. including *C. jejuni* and *C. coli* were isolated from 47.5% of chicken and 2.7% of human samples [27]. Chickens and humans isolates were genetically similar signifying the high possibilities of zoonotic transmission from animals to humans [20,28]. Isolation of

Campylobacter from diarrheic children was more frequent (17.2%) than *Salmonella* (3%), *Shigella* (2%), or other bacterial pathogens (1%) [29]. In another governorate, 59 *C. jejuni* and/or *C. coli* isolates were recovered from diarrheic humans. The isolates belonged to 14 groups for *fla*A and 11 groups for *fla*B genes indicating considerable genetic variability among isolates belonging to the same serogroup [30].

2.2. Salmonellosis

Salmonellosis is a very common zoonotic infection which may be mild or severe life-threatening disease. Salmonella, the causative agent, is gram-negative bacilli belonging to the family *Enterobacteriaceae* and has 2 species: *Salmonella bongori* and *Salmonella enterica*. The latter has over 2500 different serotypes or serovars. *Salmonella enterica* serovar Enteritidis is the major cause of human salmonellosis outbreaks in the United States and Europe [31,32]. Live animals and consumption of contaminated food of animal origin (e.g., eggs, meat, poultry and milk) have been implicated in transmission of the bacterium to humans. Also, human-to-human transmission through the fecal-oral route is possible [33,34].

Salmonella enteritidis was isolated from chickens and different animals in Egypt [33]. Salmonella infection in poultry including commercial broilers in northern Egypt during 2014–2015 [35], in eastern Egypt during the period of December 2009 to May 2010 [36] and from different markets in south of Egypt were described [37]. A highly prevalence of eggshell contamination in laying hen flocks infected with *Salmonella enteritidis* was reported [38]. In Cairo, surveillance in pigeons indicated the spread of *Salmonella* serotype Typhimurium, Braenderup and Lomita which also endanger the public health [39]. Moreover, *Salmonella* spp. was recovered from diarrheic neonatal calves [40]. Infections among imported ducklings and camels were considered as an additional source for salmonellosis in Egypt [41,42].

Furthermore, *Salmonella enterica* was isolated from food samples collected from different street venders, butchers, retail markets and slaughterhouses in Egypt [43,44]. A study described the prevalence of *Salmonella* species in dairy handlers as well as milk and dairy products randomly collected from different dairy farms and supermarkets. Two stool specimens out of 40 apparently healthy dairy handlers were positive by PCR [45]. *Salmonella* was also detected in 9.8% of the 225 seafood samples tested [46]. It is worth mentioning that typhoid fever is endemic in Egypt; and quinolones are the empirical treatment of choice. There are limited data reporting quinolone resistance among Egyptian typhoidal *Salmonella* isolates [47,48]. However, 68% of *Salmonella enterica* isolates showed multidrug resistance phenotypes [43] particularly against chloramphenicol and trimethoprim-sulfamethoxazole, streptomycin, tetracycline, ampicillin and gentamicin [49] which is of great health significance [43]. Numerous genes linked to antimicrobial resistance of *Salmonella* were prevalent in examined isolates from chicken and human origin in Egypt [49].

2.3. Brucellosis

Brucellosis remains one of the major zoonotic infections worldwide [50]. The disease is caused by a gram-negative coccobacillus bacterium of the genus Brucella, firstly discovered in 1887 by David Bruce. Since then, a number of species have been identified: for instance *B. abortus* in cattle, *B. melitensis* in sheep and goats and *B. suis* in pigs [51,52]. In animals, brucellosis causes economic losses because of abortions, decreased milk production, sterility, and veterinary care and treatment costs [51]. In humans, infection can be long lasting and is accompanied by flu-like illness with or without neurological and genitourinary complications. Zoonotic infection occurs after the contact with animals or animal products contaminated with the bacteria. Although brucellosis is a neglected disease in developed countries, it remains a major challenge for animal and human health in developing countries particularly in the Mediterranean basin, Asia and Latin America [53].

In Egypt, brucellosis was first described in 1939 [53]. Mass vaccination of animals and test-and-slaughter of serologically positive animals are the main control tools costing over $3 million annually [54]. Nevertheless, Brucella became endemic. There are limited data on the prevalence of brucellosis in animals and humans in Egypt [54]. The infection of sheep and goats by *B. melitensis* and cattle and buffaloes by *B. abortus* has been frequently reported [53,54]. In 2016, the prevalence of animal and human brucellosis was 7% and 1.25%, respectively, at a district located in the Nile Delta with high livestock density [55]. In another serosurvey in East of Egypt, 4.42% and 8.91% in private farms and individual cases, respectively, were found positive. *Brucella melitensis* biovar 3 was isolated from seroreactive animals [56]. In the period between 2006 and 2008, the prevalence of brucellosis among sheep, goats and cattle flocks in 18 Egyptian governorates were 26.7%, 18.9% and 17.2%, respectively [57]. In humans, up to 70 persons per 100,000 population were found positive to *Brucella* in 2002 and 2003; 70% were male with a median age of 26 years. The infection was associated with close contact to animals and consumption of unpasteurized milk products [58].

2.4. *Escherichia coli*

Escherichia coli is gram-negative facultative bacteria that belongs to the family *Enterobacteriaceae*. Although it is normally commensal in nature and animals, many strains are food- and waterborne zoonotic pathogens. Some strains like O157 and other enterohemorrhagic *E. coli* (EHEC) cause no discernible disease in their animal reservoirs; however, diarrhea, hemorrhagic colitis, and hemolytic uremic syndrome are not uncommon in humans [59].

In Egypt, many studies have shown a high prevalence of *E. coli* O157 strains in dairy and meat products in different locations [44,60,61]. Avian pathogenic *Escherichia coli* (APEC) infection is responsible for great economic losses in poultry industry. Avian *E. coli* strains from broiler flocks in Egypt were genetically similar to *E. coli* associated with human infection [62] with prevalence rate in chicken visceral and human stool samples of 26.9% and 46.2%, respectively [63]. Enteropathogenic *E. coli* (EPEC), diffuse-adhering *E. coli* (DAEC) and enteroaggregative *E. coli* (EAEC) are associated with infantile diarrhea in Egyptian children where 220 enteroadherent *E. coli* were identified from 729 diarrheic children [64]. In another study, *E. coli* was isolated from 52.1% hospitalized patients and 60.4% from outpatient clinics with high degrees of resistance to ciprofloxacin and co-trimoxazole [65]. Also, there is increasing incidence of carbapenemase- and extended-spectrum β-lactamase-producing *Enterobacteriaceae* in dairy farms and hospital-acquired infections. This represents a major health problem because of the few therapeutic alternatives [66].

2.5. *Listeriosis*

Listeriosis is one of the foodborne pathogens with high fatality rate. It is caused by *Listeria monocytogenes*, a gram-positive bacterium which is able to grow at temperatures as low as 0 °C challenging the control in human foodstuffs. *L. monocytogenes* can persist for long periods in the environment or as an asymptomatic infection in adult animals and birds. Neurological disorders due to encephalitis are the most common clinical signs in ruminants, in addition to late abortion. Consumption of raw milk, cheeses, raw-meat products, poultry and fish is the major sources of infection. Human listeriosis is associated with serious invasive illness, particularly in elderly and immunocompromised patients, pregnant women, newborns and infants [67].

In Egypt, existence of the organism in water [68,69], contaminated food [70], seafood [71], milk products and milk samples from apparently healthy buffaloes, cows, she-camels, goats and sheep has been reported [72–75]. During 2013, *Listeria* spp. was detected in 47.5% of 200 poultry farm samples in Egypt [76]. The isolation rates of *L. monocytogenes* from different localities in Egypt were 8% in beef burger, 4% in minced meat and 4% in luncheon meat; while sausage samples were all negative [77]. In humans, *L. monocytogenes* is considered the most common lethal complication in Egyptian patients with liver cirrhosis associated with ascites [78]. Detection of the organism in stool samples of hospitalized Egyptians was reported in different localities [71,79].

2.6. *Q Fever*

Q fever is a zoonotic bacterial disease with public health implications. The disease is caused by *Coxiella burnetii*, a gram- negative bacteriumthat mostly affect ruminants. The bacterium causes abortion in sheep, goat and cattle and is excreted in infected animal feces, urine, milk, and birth products. People can get infected by inhalation of contaminated materials. *C. burnetii* causes febrile flu-like illness and pneumonia in poor hygiene settings. The epidemiology of Q fever in Africa is poorly understood [80,81].

The epidemiology of *C. burnetii* in Egypt is not well-known [82]. Antibodies were detected in Egyptian donkeys, goats, sheep, pigs, dogs and rats [83]. Q fever may be enzootic in cattle in northern Egypt [84]. In 2006 and 2011, *C. burnetii* antibodies were detected in up to 32.7%, 23.3%, 13.3% and 13% of sheep, goats, camels and cattle samples in different localities in Egypt, respectively [82,85,86]. However, all seropositive animals were negative for *C. burnetii* DNA by PCR [85]. In 2009, the prevalence of *C. burnetii* in blood samples collected from domestic and imported livestock slaughtered at the abattoir in central Egypt was 4% in buffalo, 8% in sheep, and 70% in camels [87]. The prevalence of antibodies to *C. burnetii* among Egyptians in various locations was 5 to 28% particularly among cattle workers, veterinarians and veterinary assistants and those live in agricultural districts [82,88,89].

3. Parasitic Zoonosis

3.1. Schistosomiasis

Schistosomiasis is the second most common parasitic infection globally after malaria [90] and considered as one of the Neglected Tropical Diseases (NTDs) [91]. Schistosomiasis was reported in more than 200 million people in 74 countries and nearly 800 million people are at risk of infection worldwide [90,92]. Humans acquire the infection by contact with or drinking of contaminated water. There are three main species infecting humans including *S. mansoni*, *S. haematobium* and *S. japonicum* complex (*S. japonicum* and *S. mekongi*) [93]. Infection with *Schistosoma* spp. results in skin rash or itching, flu-like illness and severe intestinal and urinary tract disorders [94,95]. Chronic schistosomiasis can persist for years and lead to neurological complications and death [96,97].

Schistosomiasis is one of the most endemic parasitic diseases in Egypt. The earliest case of human schistosomiasis (*S. haematobium*) occurred more than 5000 years ago in an Egyptian adolescent [98]. In addition, *S. haematobium* calcified eggs were identified in two mummies aged 3000 and 4000 years old of the 20th Dynasty [99,100]. Between 1935 and 2010, the infection rate was very high in school-age children and the infection can persist among adults [95,101,102]. Furthermore, working in agriculture is a risk factor for *Schistosoma* spp. infection [103]. The prevalence of *S. haematobium* and *S. mansoni* in Egypt ranged between 0.08% and 75% [104–117]. The highest prevalences of *S. haematobium* were detected in lower Egypt [106,109], while the highest prevelance of *S. mansoni* was detected around central Egypt [102,118,119]. The overall prevalence of schistosomiasis in Egypt declined year by year to reach 10% in 1999, 5% in 2000, 3.5% in 2002, 1.2% in 2006 and 3–10% in 2010 [102,120–122]. This continuous decrease was due to the control of schistosomiasis by using praziquantel in mass chemotherapy and due to snail control by using anti-bilharzial chemotherapy [102,123,124].

3.2. Fascioliasis

Fascioliasis is caused by a liver fluke belonging to genus *Fasciola* (*Fasciola hepatica* and *F. gigantica*). *Fasciola* is one of the neglected foodborne trematodes that infect ruminants and humans worldwide [125–127]. It was estimated that fascioliasis, associated with other diseases, especially schistosomiasis, affects at least 2.4 million people in more than 70 countries [128–130]. It causes gastrointestinal problems and chronic fascioliasis results in jaundice and inflammation of the liver, gallbladder and pancreas [129]. Fecal excretion of eggs from infected animals (e.g., cattle, sheep, buffaloes, donkeys and pigs) in fresh-water is the main source of infection. After hatching, larva lodge in a particular type of water snail (the intermediate host). Carrier animals are infected by eating metacercaria encysted on leaves of water plants or vegetables [127].

Egypt is one of the endemic areas with fascioliasis in the world [131] with annual loss in milk and meat being estimated to be 30% [132]. The climatic factors influence the incidence of fascioliasis and all snail transmitted parasites in Egypt [128,133]. *F. gigantica* is considered the endogenous fasciolid species in Egypt with tropical and subtropical distribution [134] while *F. hepatica* originated from Europe and introduced to Egypt through the importation of domestic animals [135,136]. *Fasciola* spp. infected different animal species in Egypt including; sheep, goats, cattle, buffaloes, horses, donkeys, camels and rabbits and the infection rates reach 90% in some areas [137,138]. The overall prevalence in Egypt is unknown because reports show wide variations in infection rates [139]. Between 1959 and 2016, the prevalence of *Fasciola* spp. among different animal species in different localities in Egypt ranged between 0% and 59% [138–146]. In 1988, fascioliasis has been reported in approximately all Egyptian governorate where up to 60% of cattle and buffaloes and 78% of sheep were positive [139].

Since 1980, human fascioliasis was reported in most of the Egyptian governorates especially in the Nile Delta [130,139]. It was estimated that 830,000 humans are infected and 27 million of persons are exposed to the risk of infection in Egypt [147]. Between 1958 and 2006, fascioliasis has been reported in humans in different localities in Egypt and the prevalence rate was between 2% and 19% [130,139,148–153]. From 1998 to 2002, the prevalence of fascioliasis in the treated endemic areas was reduced from 5.6 to 1.2% [154]. This decrease in the prevalence was continued in 2009 to reach 0% [142]. However, in 2013, the prevalence increased again to reach 8% [155,156]. Triclabendazole is the selective treatment of fascioliasis in specific high-risk age groups such as school children and villagers [154].

3.3. Cryptosporidiosis

Cryptosporidiosis is a zoonotic protozoal disease caused by the genus *Cryptosporidium* [157]. *Cryptosporidium* spp. was discovered by Tyzzer in mice [158] and the first human case was reported in 1976 [159]. Afterwards, more attention was given to cryptosporidiosis since it was determined to cause death in one acquired immune deficiency syndrome (AIDS) patient [159]. Cryptosporidia essentially entered veterinary medicine only in the early 1980s with reports of cryptosporidium-associated neonatal calf diarrhea [160] and established as a primary enteric pathogen [161]. The importance of *Cryptosporidium* as a public health problem began in 1993, when more than 400,000 residents in Milwaukee, WI, USA were affected by *C. hominis* due to the consumption of contaminated drinking water. This was reported as the largest world waterborne outbreak [162–164]. Out of 26 *Cryptosporidium* species, *C. hominis* and C. parvum are responsible for more than 90% of human cases of cryptosporidiosis [165], exhibiting acute self-limiting diarrhea in immunocompetent persons and life-threatening diarrhea in immunocompromised persons [166]. It was estimated that 1 to 10% of the developing countries' populations were infected with *Cryptosporidium* particularly among 1-to-9-year-old children and toddlers [167].

Reports on cryptosporidiosis in Egypt are rare. The highest prevalence rates were reported in rural areas where there is close contact with animals. The accuracy of the reported prevalence rate depends on the used detection method [168]. In animals, from 1999 to 2016 the prevalence rate of *Cryptosporidium* infection ranged between 2% and 69% among different species including cattle, buffalo calves, camels, sheep, goats, lambs, dogs, wild rats and quails. The highest prevalence rates were reported in governorates that located close to the River Nile [169–181]. In humans, between 1989 and 2016 *Cryptosporidium* infection has been reported in almost all Egyptian governorates with prevalence rates ranged between 3% and 50% or up to 91% in immunocompromised patients and diarrheic children [169–171,181–197].

3.4. Giardiasis

Giardiasis is caused by *Giardia duodenalis* (syn. *G. intestinalis*, *G. lamblia*) and considered one of the most common intestinal protozoal parasites affecting humans worldwide [198]. It also infects other mammals, including pets and livestock [199]. The high-risk group is children, especially those in daycare settings, orphanages and primary schools [200] with 2.5 million annual cases in the developing countries [201]. Infection with *Giardia* spp. results in gastrointestinal disorders [200]. *Giardia* cysts can be transmitted to humans through ingestion of contaminated water or food, but the parasite can be transmitted directly from infected individuals [202]. *G. duodenalis* has been divided into eight different assemblages (A–H) that have varied host specificities [203]. Assemblages A and B have been found to infect humans and other mammals [200].

In Egypt, few studies have been done to identify the relation between different assemblages and the presence of symptoms, especially among children and animals [204,205]. Between 2004 and 2016, the prevalence of *Giardia* spp. ranged between 2% and 53% among different animal species including ruminants, dairy cattle, stray cats, wild rats and fish [152,204,206–208]. Assemblage E was also more prevalent among ruminants and dairy cattle [204,206]. In humans, between 2001 and 2017, Giardiasis has been reported in different localities of Egypt and the prevalence rates ranged between 10% and 75% [152,192,204,206,209–216]. The most prevalent *G. duodenalis* genotypes were assemblage A and B and to lesser extent assemblage E among diarrheic patients in Egypt [204–206,209,214,215,217–220]. The prevalence of *G. duodenalis* was high in rural areas more than in urban areas which was attributed to the higher exposure to multiple risk factors such as poor water supply, poor sanitation, and presence of animals [204]. Interestingly, asymptomatic Giardia infection can persist for 4 months with 4.5 episodes per child/year in rural areas in Egypt [213].

3.5. Toxoplasmosis

Toxoplasma gondii (*T. gondii*) is one of the most important human zoonotic protozoan parasites, infecting one third of the world's population [221]. Infection with *T. gondii* is prevalent in humans and animals, including poultry [222]. Cats are considered the key host in the transmission of *T. gondii* to humans and other animals as they excrete the environmentally resistant oocysts in their feces [223]. Human infections occur through ingestion of food or water containing viable cysts [224], congenitally, by blood transfusions or organs transplantation [225]. The high risk groups are immunocompromised patients and fetuses whose mothers acquire acute infection during pregnancy [226]. Infection with *T. gondii* is asymptomatic in immunocompetent and primary infected pregnant women; however, severe complication and death have been also reported [224,226–228].

In Egypt, indoor and outdoor cats are allowed to roam, where they hunt their own food or live on scraps of garbage. Therefore, the environment is highly contaminated with oocysts excreted by these cats. This might affect livestock that will later be slaughtered for human consumption [229]. In 1980s, seroprevalence of the parasite ranged between 16% and 59% in stray and domestic cats [230–232] while in 2008, antibodies were reported in 57% of cats [233]. Recently, seroprevalence of *T. gondii* was up to 98%, indicating high environmental contamination with oocysts [207,229,234]. Furthermore, *T. gondii* antibodies were detected in 10% to 62% of ruminants, including cattle, sheep and goat and in equines, including horses and donkey [235–240]. Between 1990 and 2016, seroprevalence of *T. gondii* in chickens, turkeys and ducks ranged between 9% and 85% in different localities in Egypt [241–246]. Therefore, consumption of undercooked poultry meat may be considered a risk factor for toxoplamosis in humans or animals [222]. In humans, there are limited data on the prevalence of *T. gondii* and associated risk factors in women during pregnancy. In different Egyptian localities, between 1993 and 2016, the prevalence of toxoplasma antibodies were ranged between 27% and 68% in pregnant women [236,239,245,247–253], 26% in cerebrospinal fluid of meningoencephalitis patients [254], 59.6% in asymptomatic blood donors [255].

4. Viral Zoonosis

4.1. Influenza

Influenza A viruses (IAV), members of the RNA family *Orthomyxoviridae*, have up to 144 subtypes according to the variation/combination of the surface glycoproteins hemagglutinin and neuraminidase. IAV are further classified to human influenza, swine influenza (SIV), bat influenza, equine influenza and avian influenza viruses (AIV). SIV and AIV transmit from swine or birds to humans, respectively, mostly via direct contact with infected animals. The infection in humans ranges from mild self-limiting respiratory-like illness to death [256,257].

Due to the very low pork production in Egypt, swine influenza is not a major ZD, although serosurveillance indicated infections of humans in 1979–1980 [258]. On the contrary, AIV are very important zoonotic viruses in Egypt. Poultry industry in Egypt was estimated in 2006 to be one billion birds with several millions of labors. In late 2005, the Asian highly pathogenic (HP) AIV of subtype H5N1 was firstly detected in wild migratory birds in a northern Egyptian wetland. In February 2006, the virus transmitted to domestic commercial and backyard birds and in March the first human case was recorded. To date, the virus is endemic in Egyptian birds causing tremendous economic impact despite the mass vaccination intervention strategy [259]. Another AIV subtype is H9N2 which, in poultry, did not cause severe illness unless the infection is complicated by secondary bacterial infection or immunosuppression. The endemic H9N2 in Egyptian poultry was firstly detected in 2011 and vaccination is widely used to control the infection [259].

In humans, Egypt is the country with the highest recorded cases worldwide. The fatality rate in Egypt is lower than the global rate. Thus, lower virulence and subsequent adaptation of the virus in human has been assumed. Many mutations that enhance virus binding to mammalian type receptors have been studied. Subclinical infection in human has been reported as revealed by serological surveillance [258,259]. Nevertheless, a recent study has shown that the virus has not yet acquired the aerogenic transmissibility as naïve ferrets cohoused with inoculated ferrets did not acquire infection [260]. The Egyptian H5N1 viruses are highly susceptible to antiviral drugs (Oseltamivir), but are resistant to amantadine. Infection is usually acquired by intensive contact particularly with backyard birds. Women and children are mostly affected. To date, there are 3 human infections by H9N2 viruses reported to the WHO [261]. Subclinical infection in poultry workers and co-infection of poultry and human with H5 and H9 in Egypt have been reported. Moreover, serosurvey revealed the presence of antibodies against H7 viruses in poultry [262] and in humans [263], but no virus was isolated, so far [262,263].

4.2. Rabies

The rabies virus (RABV) belongs to the genus Lyssavirus of the RNA family *Rhabdoviridae* within the order *Mononegavirales*. Rabies is a widespread neurological zoonotic disease of all warm-blooded animals including humans. Dogs are the most important host for RABV, however wild carnivores (e.g., fox) and bats are considered reservoirs. Infection in humans occurs by direct contact with mucosal surfaces (e.g., bites) or possibly through contamination of wounds with infected materials (e.g., scratches). The virus has a relatively long incubation period (according to the site of bite) which may reach a few months to a year giving the opportunity for immediate vaccination/treatment. Each year, about 60,000 fatal human infections are recorded worldwide [264,265].

In Egypt, RABV was recognized before 2300 B.C. [266]. Although the notifiable disease is now endemic in many regions throughout the country, there are no recent reported outbreaks of RABV. It is worth mentioning that the canine population in Egypt was estimated to exceed three million stray dogs and half a million owned dogs. Vaccination of dogs in Egypt was usually done by low-egg-passage of the Flury strain, which has now been replaced by attenuated tissue culture vaccines [266]. The disease transmitted to humans in Egypt mainly by dog bites, however the virus has been detected in other animals: cats, ruminants (e.g., buffaloes), horses, donkeys, rodents and mongooses [266–269]. In 1970s, the virus was isolated from several rodents and wild mammals including Gerbils, foxes and cats [270,271]. In 1988, Naval Medical Research Unit Three (NAMRU-3 is a biomedical research laboratory of the US Navy located in Cairo, Arab Republic of Egypt) isolated street RABV from dogs (n = 9), cats (n = 2), farm animals (n = 2), Gerbils (n = 3) and Jackal (n = 1). In 1990, an outbreak was reported to the OIE. In 1998–1999, there was a record for isolation of RABV from dogs in Egypt [272]. In 2012–2014, two studies reported the detection of the virus in the brain samples of water buffaloes (*Bubalus bubalis*) exhibiting fever and/or nervous signs. The infection was acquired mostly after being bitten by a fox. The virus was closely related to other street strains of dogs in Egypt, Israel and Jordan [267,273]. In 2015, RABV was isolated from brain tissue of an adult female dog. The dog developed hypersalivation, paralysis, and hyperesthesia consistent with rabies symptoms. The virus was genetically similar to canine RABV circulating in Egypt [274].

Reports of human infection in Egypt have been described from 1904 to 2000s [266] and 30 to 40 annual deaths due to RABV was reported [269,275]. In 1979, a French woman died after corneal transplantation from an Egyptian donor [276]. In 1988, NAMRU3 isolated two street RABV from humans [268]. Genetically, the Egyptian viruses from humans and animals are closely related to those isolated in Israel and the ME [272]. Lastly but not least, the huge number of stray dogs roaming freely with livestock and insufficient vaccination coverage of pets are among the most common hallmarks of the endemic status of RABV in Egypt.

4.3. Rift Valley Fever

Rift Valley fever (RVF) is a vector-borne zoonotic viral disease firstly reported among livestock in Rift Valley of Kenya in the early 1900s. The disease is caused by a RVF virus (RVFV), genus *Phlebovirus*, a member of the RNA family *Bunyaviridae* and was first isolated in 1931. The virus infects mosquitoes, which act as a reservoir, while animals and humans are considered amplifying hosts. RVFV infects a wide spectrum of mammals, causing abortion and mortality. In humans, symptoms range from mild fever, muscle pains and headaches to hepatic failure and death. Direct contact to infected animal blood, aerosol, drinking unpasteurized contaminated milk, or the bite of infected mosquitoes are the major sources for human infection. Vaccination of susceptible animals, restriction of movement (e.g., importation) and reduction or control of mosquitoes' population are the regular control measures. The disease is common in Africa and the ME [277,278].

In the last 40 years, Egypt reported five large outbreaks: in 1977–1978, 1993–1994, 1997, 2000 and 2003 and the largest epizootic was in 1977–1978 [279–284]. The primary introduction of RVFV into livestock in these outbreaks in Egypt was mostly linked to importation of animals mainly camels from Africa [280,282,284–287]. The virus was isolated from various species of domestic animals (e.g., sheep, cows, buffaloes, camels, goats, horses, and rats) as well as humans [288,289].The epizootics of RVF in Egypt were reported every year round. The effects of rainfall and river discharge in addition to optimal constellation of interconnected hydrologic, entomologic (high mosquitoes' populations), and social conditions were incriminated in the spread of the virus [286,290–295]. Moreover, anti-RVFV antibodies were detected in pigs in 2008 [296], domestic and imported cattle and buffaloes in 2009 [87] and non-immunized dairy cattle from different localities in Egypt in 2013–2015 [297]. The reoccurrence of RVF outbreaks from time to time in animals in Egypt challenges the importation control check points and the efficacy of the applied vaccination program [280,281].

In humans, in 1977, RVFV in Egypt caused huge outbreaks including 200,000 human infections and 600 deaths [282,298–304]. The virus transmitted to eight Swedish United Nations Emergency Forces soldiers serving in Egypt and the Sinai Peninsula [305]. Possible human-to-human transmission was described [302], however the infection mostly occurred by handling infected meat and inhaling natural virus aerosols [287,306]. In 1993, in southern Egypt, 600–1500 human infections associated with ocular disease, fever and headache were reported [279,307]. Serological surveillance indicated that workers at abattoir and sewage treatment plants in several governorates of Egypt possessed RVFV antibodies without showing clinical signs [308,309]. Moreover, in 2008, RVFV antibodies were detected in ~14% of veterinarians and their assistants, butchers and abattoir workers in pigs' abattoir [296].

4.4. MERS

Middle East Respiratory Syndrome (MERS) caused by a newly emerging coronavirus (CoV), designated lineage C of Betacoronavirus, in the RNA family *Coronaviridae*. It was firstly reported in Saudi Arabia in a patient with respiratory illness in 2012 [310] and transmitted to several countries not only in the Middle East (ME) but also in Africa, Asia and Europe. The virus is usually transmitted from dromedary camels via direct contact or consumption of milk or medicinal use of camel urine [311]. Also, bats and alpacas were considered reservoir hosts [311,312]. However, limited human-to-human infections have been also reported. The infection can be mild or fatal in those patients with immune system disorders or chronic diseases [313].

In Egypt, out of 110 swabs and 52 serums collected in June–December 2013 from clinically healthy imported or locally reared camels in abattoirs, 4 and 48 positive samples were detected, respectively. Attempts to isolate the virus in cell culture were not successful. None of 179 samples collected from workers in these abattoirs were positive by RT-PCR [314]. In another study, in June 2013, all serum samples collected from humans, cows, water buffaloes, goats and sheep were negative for MERS-CoV antibodies. Conversely, 94% of serum samples collected from dromedary camels were positive for MERS-CoV [315]. From June 2014 to February 2016, 2541 sera, 2825 nasal swabs, 114 rectal swabs, 187 milk samples, and 26 urine samples were collected from camels in different sectors in Egypt (importation quarantines, markets, abattoirs, free-roaming herds and farmed breeding herds). Results revealed 71% seropositivity and 15% of other samples were positive by RT-PCR. Seroprevalence was 90% in imported camels and 61% in locally raised camels, likewise RNA detection rates were 21% and 12%, respectively. Both juveniles and adult camels were positive by 82% and 37% seropositivity and similar RT-PCR detection rates of 15% and 16%, respectively [316].

In humans, from 2012 to 2015, none of nasopharyngeal and oropharyngeal swabs collected from 3364 returning Egyptian pilgrims were positive for MERS-CoV [317]. To January 2017, only one human case was reported from Egypt in April 2014 [318].

4.5. Crimean-Congo Hemorrhagic Fever (CCHF)

Crimean-Congo hemorrhagic fever (CCHFV) is a tick-borne virus from the *Bunyaviridae* family. The virus causes severe hemorrhagic fever outbreaks, with a case fatality rate of up to 40%. It is endemic in some African, Middle Eastern and Asian countries. Farm animals like sheep, goats, cattle, camels and ostriches can be infected without showing any clinical signs. Ticks of the genus *Hyalomma* are the principal vector. Humans and animals become infected after being bitten by ticks. Also, animal to human transmission through contact with infected animal blood or tissues, particularly at the abattoirs are common. Therefore, veterinarians, agricultural workers and slaughterhouse workers are most affected [319].

In Egypt in 1976, the antibodies to CCHFV detected in 8.8% camels sera and in 23.1% sheep sera but no antibodies were detected in sera from equines (donkeys, horses and mules), pigs, cows, and buffaloes [320]. In 1986–1987, 14% of serum samples collected from imported camels from Sudan and Kenya into Egypt was positive for CCHFV antibodies. Native livestock including sheep and cows were negative [321]. Between September 2004 and August 2005, 3.83% of cattle, 0.38% of water buffalo, 6.3% of sheep and 1.14% of goats were positive for CCHFV antibodies [322]. In July 2009, ectoparasites removed from freshly slaughtered cattle, buffalo, sheep and camels imported from Sudan and Somalia were negative for CCHFV except five camels were found to harbor ticks carrying RNA from a new CCHFV variant [323]. In 2009 in a serosurvey in domestic and imported livestock, only one cow out of 161 was positive while buffaloes, sheep, and camels were negative for CCHFV antibodies [87].

No antibodies were detected in sera from humans in 1976 [320]. The only known human infection with CCHFV in Egypt happened in 1981. An Egyptian virologist died after mouth-pipetting a culture of a CCHFV isolate that he had brought from Iraq [324].

4.6. West Nile Fever (WNF)

West Nile is a remerging ZD caused by West Nile fever virus (WNV), a *Flavivirus* that belongs to the RNA family *Flaviviridae*. The virus was firstly identified in 1937, in Uganda. During the last decade, the incidence of WNV increased worldwide. The virus is transmitted by arthropod vectors and the mosquitoes of the genus *Culex* are main reservoirs [325]. The latter feed on birds especially passerines and thus birds become infected. Migratory birds thought to be responsible for wide spread of WNV and reintroduction from enzootic to new regions [326]. Mosquitoes-birds-mosquitos' infection is the classical transmission cycle in nature. Accidentally, human infections occur through biting or dealing with contaminated blood or tissues. The infection in birds is mostly subclinical, while humans exhibit mild, if any, illness to fatal West Nile encephalitis particularly in at-risk individuals such as the elderly, immunocompromised and people with chronic illness [327]. Seasonal incidence of WNV outbreaks is linked to higher populations of Culex mosquitoes during summer months in temperate regions and rainy seasons in the tropics. However, infections of humans have been also associated with other factors (e.g., blood transfusion, occupational exposure, etc.) [327].

The Egyptian climate is suitable for the spread of WNV [328] where more than 110 mosquito species and subspecies including Culex species were identified [291,329]. The virus was firstly isolated from mosquitoes in early 1990s [295]. In the period from 1999 to 2002, 15 (0.29%) out of 112,155 examined samples from mosquitoes and sand flies were positive for the WNV. Interestingly, the virus transmitted from mosquitoes to sentinel chickens [330]. It is worth mentioning that more than 150 species of migratory birds visit Egypt annually in addition to 350 resident species of birds [291,329]. Israeli-like WNV was isolated in white storks in Egypt in 1997–2000 suggesting that migrating birds do play a crucial role in geographical spread of the virus [331].

The first serological evidence for human infections with WNV in Egypt were reported in 1950 in 22% of children and 61% of adults included in a study conducted by Melnick et al. [332]. In 1968, 14.6% of hospitalized febrile children were linked to WNV infection [333] and 5 out of 133 patients suffering from aseptic meningitis or encephalitis possessed WNV antibodies [334]. In 1969, approximately half of 1113 male University students and 3% of 162 patients in different localities had WNV antibodies [335,336]. Between 1984 and 1985, one out of 55 patients with non-specific fever and myalgia was positive for WNV [337]. In 1989, 3% of school children aged 8–14 years [299] and 45.5% out of 180 examined persons in the Nile Delta were positive for WNV antibodies [338]. WNV had the highest prevalence (54.14%) among other viruses in a serosurvey targeting workers in sewage treatment plants from January to October 1999 [309]. In early 2000s, a Dutch 44-year-old female was infected during a holiday in Egypt [339]. In 1999–2002, WNV was actively circulating in different areas in Egypt causing febrile illness and up to 24% of human serum samples were positive [330]. Currently, the disease is mostly underestimated and scarce data are available, so far.

5. Summary and Conclusions

In this review, some aspects of viral, bacterial and parasitic diseases with zoonotic importance in Egypt were summarized. There is a gap of knowledge about the epidemiology of zoonotic diseases in different localities in Egypt, which hinders accurate assessment of the human health burden. Surveillance activity is high for some viral diseases such as influenza and MERS but is still weak or neglected for others particularly at the human-animal interface. Control of diseases in animals depends on the vaccination (e.g., against RVFV, AIVs), anti-microbials for bacteria and antiprotozoal medication against parasitic infection. While some pathogens/diseases are exotic in Egypt (e.g., MERS-CoV and RVFV acquired by importation of camels or WNV from wild birds), others are endemic (e.g., AIV, Rabies, *Schistosoma*, and *Fasciola*). Transboundary transmission of zoonotic agents from Egypt to Europe, Asia and America occurred via different pathways. RABV was reported in the US via falsified vaccination certificate of dogs [274], in Europe via corneal transplantation from an Egyptian donor [276] and in Asia, probably by dog transfer [272]. Also, RVFV infected Swedish soldiers on duty in Egypt in 1977 and 1978 [305]. Egyptian AIV was reported in poultry in neighboring countries most likely due to smuggling of poultry or migratory birds [340]. Approximately 100,000 Egyptians travel to Saudi Arabia in pilgrimage, every year, which is an important risk factor for possible introduction or spread of infections [341].

There are several suggestions to improve the control of zoonoses in animals and humans in Egypt. Enhancing biosecurity and management in animal farms particularly in poultry sectors may reduce the risk of salmonellosis, campylobacteriosis, listeriosis and influenza viruses. Multidrug-resistance of bacteria in animals, due to the misuse of antibiotics in the veterinary sector, is an increasing problem in Egypt. Therefore, regulations for antibiotic application in animals must be enforced to mitigate the serious public health hazard. Vaccination as an alternative approach for the control of bacterial infections in animals, vaccination of stray dogs against RABV and regular investigation of cats for toxoplasmosis should be considered. Longer quarantine periods or restriction of importation of animals, particularly camels, from endemic countries may be effective to reduce introduction of zoonotic viruses. Control of vectors (e.g., mosquitoes), intermediate hosts (e.g., snails) and animal reservoirs (e.g., stray dogs, cats) should be key components in the intervention strategy of zoonoses in Egypt. Improving, providing and upgrading diagnostic techniques in both veterinary and human medicines are fundamental to early detect and contain zoonotic infections. Last but not least, sustainable awareness, education and training targeting groups at high risk (veterinarians, farmers, abattoir workers, nurses, etc.) are of great importance to reduce the burden of zoonoses among Egyptians. Taken together, there is an urgent need for collaborative surveillance and intervention plans for the control of zoonotic diseases in Egypt.

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