Global Variations and Changes in Patterns of Infectious Uveitis

1

François Willermain, Yves Van Laethem, and Laure Caspers

1.1 Introduction

Before 1940, most uveitis cases were supposed to be due to infectious agents, mainly syphilis or tuberculosis [1]. Progress in the understanding of intraocular inflammation led to the discovery that uveitis can be of infectious and noninfectious origin and that many pathogens can cause infectious uveitis. Theoretically, Koch postulates must be fulfilled, in order to formerly demonstrate that a disease is due to an infectious agent. However, in infectious uveitis, most often, serological evidence, molecular or histological demonstration, and treatment response are usually the only available elements to suggest the infectious origin of the uveitis. Using these evidence a large number of infectious organisms have been demonstrated to cause infectious uveitis. Some have a global importance around the world, while others have more limited niches. Many of them have been considered as emerging pathogens.

F. Willermain (✉)
Department of Ophthalmology, CHU St-Pierre, Bruxelles, Belgium
e-mail: fwillerm@ulb.ac.be

Department of Ophthalmology, CHU Brugmann, Bruxelles, Belgium

Y. Van Laethem
Department of infectious diseases, CHU St-Pierre, Bruxelles, Belgium

L. Caspers
Department of Ophthalmology, CHU St-Pierre, Bruxelles, Belgium

According to Woolhouse, an emerging pathogen can be defined as an infectious agent whose incidence is increasing following its introduction into a new host population. A pathogen will be reemerging when its incidence increases in an existing host population [2]. However, in practice, both expressions are likely used by many authors regardless of those biological and epidemiological criteria. The term emerging disease will thus also be used in situation of increase awareness or discovery of pathogen in previously supposed non-infectious diseases [2]. As far as we know, most emerging infectious uveitis agents fall into the two last categories.

1.2 Emerging Disease

1.2.1 Origin of Human Infectious Disease

By definition, the question of emerging infectious disease addresses how a microbe becomes a pathogen in the human species. Emerging infectious disease thus resumes the origin of human infectious disease. Most of the emerging infections discovered during the last decades are zoonosis. Major modifications in human behavior have facilitated their jump from animals to humans. The global population has increased from 600 million humans around 1700 to 1.5 to 1.8 billion in 1900, 6 billion in 1998, and more than 7 billion in 2015. More than 50 % of those people reside in urban areas (from 40 % in

S.-P. Chee, M. Khairallah (eds.), *Emerging Infectious Uveitis*, DOI 10.1007/978-3-319-23416-8_1

Africa to 80 % in the Americas), in contrast with only 30 % in 1950. Environmental modifications were mandatory to build those cities, with deforestation or other forms of land use than in the past. Therefore, and also linked to widespread international trade of goods and animals, microbes have received a new and rapid access to an ever larger human population. In addition, the population is globally more mobile also; international travel rose above one billion people in 2012, further increasing pathogen dissemination around the globe.

In the past decades, most new pathogens were acute respiratory viruses. For instance, human metapneumovirus (first reported in 2001 in the Netherlands but demonstrated thereafter in specimens stored since the 1950s at least) is a paramyxovirus leading to very frequent and sometimes very severe respiratory tract infections in small children [3]. A new betacoronavirus is the agent of SARS (severe acute respiratory syndrome), discovered in 2003 after a physician infected a dozen patients in Hong Kong, with subsequent more than 8,000 cases in 29 countries and 774 deaths [4]. Another new coronavirus (MERS-CoV, Middle East respiratory syndrome coronavirus) has been demonstrated as the causative agent of a deadly respiratory tract infection in the Middle East since 2012, with more than 1,000 cases and 400 deaths [5]. But of all these emerging pathogens, the flu viruses, are the most widespread and deadly. Influenza A is a zoonose, with viruses mutating and mixing in swine and birds. If the Spanish flu (new H1N1 influenza A virus) killed more than 50 million people in 1917–1918, several pandemics (H2N2 in 1957, H3N2 in 1968, and new H1N1 in 2009) appeared in the more recent decades, with a lower but consequent mortality. In more restricted areas, non-pandemic strains of influenza A as H5N1 (Asia and Egypt) or H7N9 (China) are still potential deadly sword of Damocles [6].

1.2.2 The Birth of a Human Infectious Disease: Example of the AIDS Story

One of the most severe emerging infections of the last centuries is obviously AIDS (acquired immunodeficiency syndrome) linked to the HIV1 (and rarely HIV2) [7]. If it was first recognized in 1981 in the United States, its emergence in the human world is older and faraway from our Western World. Indeed, the oldest known case (a posteriori) is a man in the present Democratic Republic of Congo, in 1959. Analysis of the virus in his frozen serum as well as others suggests that HIV1 and HIV2 were separately acquired from monkeys in the 1930s, in the western part of Central Africa. In more than 40 SIV (simian immunodeficiency viruses) presently known, only HIV1 and HIV2 were able to infect humans and to establish persistent human to human transmission. Here again, urbanization and increasing local/regional trade, with all the sociologic modifications that it implicated, have largely contributed to the dissemination of the disease in sub-Saharan Africa. In a second time, international travel, sexual behaviors, and IV drug abuse have been keystone factors in the worldwide propagation of AIDS [8].

1.3 Re-emerging Disease

If emerging disease brings us to the origin of infectious disease, re-emerging disease deals with the evolution of infectious disease and the impact of the human society on it. Most of those reemerging infections are also zoonoses, often linked to a vector. Climatic changes (global warming) have allowed ticks to reach higher latitudes as well as altitudes, with transmission of Lyme disease or tick-borne encephalitis more in the north of Scandinavia or at higher altitude in Central Europe [9–11]. Similarly, mosquitos as *Aedes albopictus* are now found in the south of Europe (as France and Italy), with several local transmissions during the summer of dengue or chikungunya from imported cases. Chikungunya virus was discovered 60 years ago in Tanzania and since that time has spread to several parts of Africa and in all Indian Ocean/Western Pacific countries [12, 13]. Due to the introduction by an international traveler of an Asian strain in the Caribbean in 2014, Chikungunya is now an important public health problem not only in those

islands but already also in Central and South America [14]. West Nile virus infection was unknown in the Americas until 1999. Due to migration from the Old World of birds wearing infected ticks, the infection was introduced in the northeast of the United States, and in a few years, it spread to all the States [15].

1.4 Variation in Patterns of Infectious Uveitis

1.4.1 Introduction

Few studies, and mainly from the occidental world, address the incidence and prevalence of uveitis [16]. It is therefore difficult to raise conclusions on global variations or evolution of this epidemiological aspect of intraocular inflammation. This contrasts with the important literature describing the causes of uveitis in different center and location in world which clearly shows important variations of the distribution of different etiologies around the globe. Those differences are mainly due to genetic and environmental factors and often grouped between the so-called developed and developing worlds. Accordingly, the distribution of both specific infectious and noninfectious causes varies greatly around the world.

In the context of infectious uveitis, some uveitis type is logically limited to endemic regions. Onchocerciasis, for example, has a limited distribution in Africa, South America, and Yemen [17]. Lyme disease is almost exclusively found in the Northern Hemisphere. Leptospirosis occurs most frequently in tropical and subtropical area. Brucellosis remains prevalent in the developing world, mostly in the Mediterranean Basin, the Arabic Gulf countries, India, and Central America. HTLV-1 infection is endemic in the Caribbean, Central and South America, South and Intertropical Africa, and Japan. Similarly other infectious agents such as dengue, West Nile virus, Rift Valley fever, or chikungunya virus, as well as rickettsia only infect patients in limited endemic regions. There are thus only reported as causes of uveitis in studies from those regions. In the series of Rathinam SR and Namperumalsamy from India, leptospirosis was the most frequent cause of infectious uveitis but remains very rare in the United States and Europe [18, 19]. However, due to evolution in our societies, such as globalization, those causes of infectious uveitis begin to emerge in non-endemic regions in patients having traveled in endemic regions (see Sect. 1.4.2.3) [20].

In contrast some *organisms* have spread worldwide, some with a relative stable incidence and others with period of increase and/or decrease incidence. For example, across the world, toxoplasmosis and herpesvirus remain major causes of posterior and anterior uveitis, respectively [21–26]. Tuberculosis and syphilis are discussed in the next paragraph as classic examples of worldwide cause of uveitis with period of burden and decrease. An important example of decreased incidence of a ubiquitous infectious uveitis is CMV retinitis which made a steep decline in incidence following the introduction of HAART [27].

1.4.2 Emerging Infectious Uveitis

1.4.2.1 Emerging Infectious Uveitis Secondary to Pathogen Incidence Increase

In Europe, it is believed that syphilis has emerged around 1495. Interestingly, it has been reported that in its early years, the disease was much more severe that nowadays, suggesting the selection of a milder strain of *Treponema pallidum* occurred. Since that time, syphilis has continued to spread around the world and became one of the major health problems, illustrated by the fact that, in the nineteenth century, an entire medical subspecialty, syphilology, was devoted to its study [28, 29]. The discovery of penicillin has been associated with a significant decrease of syphilis rate to the point that some authors have postulated that the disease might disappear. Unfortunately, this was not the case and the incidence of syphilis has been the subject of important variation with frequent outbreak [29, 30]. For example, in the United Kingdom, there has been a 1032 % increase in the incidence of syphilis between 1999 and 2008. This exponential increase has been attributed to unsafe

sexual practices mainly among men who have sex with men (MSMs) [31]. The same trend was found in other countries. As a consequence, many reports have warned the uveitis community of what was called by Narsing Rao and colleague "the reemergence of an old adversary" [32, 33]. Meanwhile, a tremendous number of studies have been published improving our knowledge on the epidemiology and clinical presentation of ocular syphilis. Acute syphilitic posterior placoid chorioretinitis was in this context rediscovered with an exponential rate of publication from 1990, the year of its publication by Gass, to 2014 [34].

Tuberculosis is another old infectious disease which had a major impact on global human health. Overall, the worldwide burden of tuberculosis is still growing, as control of the disease in many regions of the world is offset by the increase incidence in another part, mainly sub-Saharan [35]. Tuberculosis remains one of the most important infectious causes of morbidity and mortality worldwide. In contrast with syphilitic uveitis, where the diagnosis can be easily made based on serological evidences, there is a great confusion regarding the diagnosis and treatment of ocular tuberculosis. Progress in systemic and ophthalmological investigation together with a more accurate description of clinical signs has permitted to better define guidelines for the diagnosis and treatment of intraocular tuberculosis [36, 37]. Nowadays, tuberculosis is a leading cause of uveitis in endemic countries, but tuberculosis uveitis can also be found in non-endemic countries with a probable recent increased frequency [24, 38–40]. This recent increment of tuberculosis uveitis in non-endemic countries is mainly attributed to the development of immigration and postulated by Llorenc and coworkers to be one of the challenges of globalization [39, 40]. There is thus an increased awareness of ocular tuberculosis among uveitis specialists all around the globe.

1.4.2.2 Emerging Infectious Uveitis Secondary to Pathogen Identification

One of the major recent breakthroughs in the uveitis field was the discovery that two entities, namely, Posner-Schlossman syndrome (PSS) and Fuchs heterochromic iridocyclitis (FHI), previously considered as idiopathic, were actually due to virus infection. Fuchs heterochromic iridocyclitis is characterized by a series of clinical signs (FHI making its classical presentation almost pathognomonic. The origin of FHI remains elusive until 2004 when Quentin CD and Reiber H elegantly demonstrated an elevated intraocular rubella antibody production in FHI, suggesting that FHI is a rubella-driven disease [41]. Four years later, de Visser et al. confirmed that rubella-positive patients presented a clinical syndrome similar to FHI [42]. As both a proof of concept and an illustration of the impact of human society on uveitis infectious epidemiology, Birnbaum et al. have demonstrated that FHI is less common in patients born since the introduction of the US rubella vaccination program [43]. At the same time, a study from the Singapore National Eye Centre, using PCR, found that CMV can also be detected in eyes with FHI [44]. More recently, Babu et al. have found in addition the presence of HSV and chikungunya virus in FHI eyes [45].

A possible role played by CMV infection in the development of PSS was suggested by early work of Bloch-Michel in the eighties [46]. Since that time, several works have confirmed this hypothesis [44, 47, 48]. In addition to PSS, it was found in those studies that CMV-positive anterior uveitis can also present the clinical characteristics of FHI or chronic granulomatous uveitis. Altogether, those data indicate that several previously thought idiopathic uveitis (PSS, FHI, and some chronic granulomatous anterior uveitis) have indeed a viral origin. This evidence has not only important implications for the epidemiology but, of course, also for the management of uveitis.

1.4.2.3 Emerging Infectious Uveitis Secondary to Increase Awareness and Better Disease Description

We have seen earlier that the success of humanity in terms of demographic expansion has create favorable conditions to increase the speed for the emergence and spreading of infectious diseases. In other terms, diseases might quickly jump between very distant part of the world and confront clinicians with diseases unusual in their

region. Fortunately, the dissemination of information has also been progressively accelerated allowing a quick exchange of information between specialist from endemic regions and recently affected countries. In this context, a series of infectious uveitis, mainly rickettsioses, West Nile virus, dengue, or chikungunya, has been the subject of an increase awareness and careful descriptions from both endemic and non-endemic regions [20, 49, 50].

The recent outbreaks of Ebola and Zika virus have been similarly associated with uveitis cases and those pathogens should be now included in the list of emerging infectious uveitis agents [51, 52].

Conclusions

The epidemiology of infectious uveitis is a dynamic process and the consequence of the complex relationship between microbes and human. On one hand, some pathogens such as toxoplasmosis or herpesvirus remain major causes of uveitis, while others, such as tuberculosis, seem to progress despite our efforts to eradicate them. On the other hand, infectious uveitis previously limited to particular geographical niches can now be found almost all around the globe. This is clearly due to evolution of our lifestyle which has also important impact on the emergence of new infectious diseases which might become someday new uveitis causes. The decrease of CMV retinitis among AIDS patients following HAART highlights that, in addition to this negative aspect, our civilization also has a positive impact on infectious uveitis epidemiology and is able to reduce the incidence of some devastating infectious uveitis causes. Indeed, we should not forget that the development of our human society has also created better ways to diagnose, control, and eventually eradicate infectious diseases.

Core Messages

The cause of infectious uveitis varies greatly around the world. Some widespread microbes continue to threaten vision in almost every part of the globe. Some infectious uveitis previously limited to particular geographical niches can now be found almost all around the globe. This evolution is the consequence of changing in our lifestyle which has also important impact on the emergence of new infectious diseases as well as their diagnosis and management.

References

1. Samson CM, Foster CS (2002) Syphillis. In: Foster CS, Vitale AT (eds) Diagnosis and treatment of uveitis. WB Sauders Company, Philadelphia
2. Woolhouse MEJ (2002) Population biology of emerging and re-emerging pathogens? Trends Microbiol 10:S3–S7
3. Hamelin ME, Boivin G (2005) Human metapneumovirus: a ubiquitous and long standing respiratory pathogen. Pediatr Infect Dis J 24:S203–S207
4. World Health Organisation (2003) Consensus document on the epidemiology of SARS. http://www.who.int/csr/sars/en/WHOconsensus.pdf
5. ECDC. Severe Respiratory Disease associated with Middle East respiratory syndrome coronavirus (MERS-CoV) 14th update Feb 2015. http://www.ecdc.europa.eu/en/publications/_layouts/forms/Publication_DispForm.aspx?List=4f55ad51-4aed-4d32-b960-af70113dbb90&ID=1264
6. ECDC. Communicable disease threats report 15–21 February 2015 week 8. http://www.ecdc.europa.eu/en/publications/_layouts/forms/Publication_DispForm.aspx?List=4f55ad51-4aed-4d32-b960-af70113dbb90&ID=1263
7. Barré-Sinoussi F, Chermann JC, Rey F, Nugeyre MT, Chamaret S, Gruest J et al (1983) Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). Science 220:868–871
8. De Cock KM, Jaffe HW, Curran JW (2011) Reflections on 30 years of AIDS. Emerg Infect Dis 17:1044–1048
9. WHO/ECDC. Joint factsheet on Lyme borreliosis. http://www.ecdc.europa.eu/en/healthtopics/vectors/world-health-day-2014/Documents/factsheet-lyme-borreliosis.pdf
10. WHO/ECDC factsheet on TBE. http://www.ecdc.europa.eu/en/healthtopics/vectors/world-health-day-2014/Documents/factsheet-tick-borne-encephalitis.pdf
11. Shuman EK (2011) Global climate change and infectious diseases. Int J Occup Environ Med 2:11–19
12. Chretien J-P, Linthicum K (2007) Chikungunya in Europe: what's next? Lancet 70:1805–1806

13. Burt FJ, Rolph MS, Rulli NE, Mahalingam S, Heise MT (2012) Chikungunya: a re-emerging virus. Lancet 379:662–671
14. Chikungunya outbreak in Caribbean region. http://www.ecdc.europa.eu/en/publications/_layouts/forms/Publication_DispForm.aspx?List=4f55ad51-4aed-4d32-b960-af70113dbb90&ID=1127
15. Jones KE, Patel NG, Levy MA, Storeygard A, Balk D, Gittleman JL et al (2008) Global trends in emerging infectious diseases. Nature 451:990–994
16. Daudin JB (2010) Epidémiologie. In: Brezin AP (ed) Les uvéites. Société Française d'Ophtalmologie: Elsevier Masson, Paris
17. Mackenzie CD, Homeida MM, Hopkins AD, Lawrence JC (2012) Elimination of onchocerciasis from Africa: possible? Trends Parasitol 28:16–22
18. Rathinam SR, Namperumalsamy P (2007) Global variation and pattern changes in epidemiology of uveitis. Indian J Ophthalmol 55:173–183
19. Shukla D, Rathinam SR, Cunningham ET (2010) Leptospiral uveitis in the developing world. Int Ophthalmol Clin 50:113–124
20. Khairallah M, Jelliti B, Jenzeri S (2009) Emergent infectious uveitis. Middle East Afr J Ophthalmol 16:225–238
21. Petersen E, Kijlstra A, Stanford M (2012) Epidemiology of ocular toxoplasmosis. Ocul Immunol Inflamm 20:68–75
22. Islam SM, Tabbara KF (2002) Causes of uveitis at the eye center in Saudi Arabia: a retrospective review. Ophthalmic Epidemiol 9:239–249
23. Khairallah M, Yahia SB, Ladjimi A, Messaoud R, Zaouali S, Attia S et al (2007) Pattern of uveitis in a referral centre in Tunisia, North Africa. Eye 21:33–39
24. Abdulaal M, Antonios R, Barikian A, Jaroudi M, Hamam RN (2014) Etiology and clinical features of ocular inflammatory diseases in a tertiary center in Lebanon. Ocul Immunol Inflamm 9:1–7
25. Jakob E, Reuland MS, Mackensen F, Harsch N, Fleckenstein M, Lorenz HM et al (2009) Uveitis subtypes in a German interdisciplinary uveitis center – analysis of 1916 patients. J Rheumatol 36:127–136
26. Sittivarakul W, Bhurayanontachai P, Ratanasukon M (2013) Pattern of uveitis in a university-based referral center in southern Thailand. Ocul Immunol Inflamm 21:53–60
27. Schwarcz L, Chen MJ, Vittinghoff E, Hsu L, Schwarcz S (2013) Declining incidence of AIDS-defining opportunistic illnesses: results from 16 years of population-based AIDS surveillance. AIDS 27:597–605
28. Knell RJ (2004) Syphilis in renaissance Europe: rapid evolution of an introduced sexually transmitted disease? Proc R Soc Lond 271:S174–S176
29. Shockman S, Buescher L, Stone SP (2014) Syphilis in the United States. Clin Dermatol 32:213–218
30. Mattei PL, Beachkofsky TM, Gilson RT, Wisco OJ (2012) Syphillis: a reemerging infection. Am Fam Physician 86:433–440
31. Mathew RG, Goh BT, Westcott MC (2014) British ocular syphilis study (BOSS): 2-year national surveillance study of intraocular inflammation secondary to syphilis. Invest Ophthalmol Vis Sci 55:5394–5400
32. Chao JR, Khurana RN, Fawzi AA, Reddy HS, Rao NA (2006) Syphilis: reemergence of an old adversary. Ophthalmology 113:2074–2079
33. Cunningham ET, Eandi CM, Pichi F (2014) Syphilitic uveitis. Ocul Immunol Inflamm 22:2–3
34. Gass JD, Braunstein RA, Chenoweth RG (1990) Acute syphilitic posterior placoid chorioretinitis. Ophthalmology 97:1288–1297
35. Maartens G, Wilkinson RJ (2007) Tuberculosis. Lancet 370:2030–2043
36. Gupta V, Gupta A, Rao NA (2007) Intraocular tuberculosis – an update. Surv Ophthalmol 52:561–587
37. Gupta A, Sharma A, Bansal R, Sharma K (2015) Classification of intraocular tuberculosis. Ocul Immunol Inflamm 23:7–13
38. Al Mezaine HS, Kangrave D, Abu El-Asrar AM (2010) Patterns of uveitis in patients admitted to a university hospital in Riyadh, Saudi Arabia. Ocul Immunol Inflamm 18:424–431
39. Jones NP (2013) The Manchester uveitis clinic: the first 3000 patients-epidemiology and casemix. Ocul Immunol Inflamm 23(2):118–126
40. Llorenç V, Mesquida M, Sainz de la Maza M, Keller J, Molins B, Espinosa G et al (2015) Epidemiology of uveitis in a Western urban multiethnic population. The challenge of globalization. Acta Ophthalmol 93(6):561–567
41. Quentin CD, Reiber H (2004) Fuchs heterochromic cyclitis: rubella virus antibodies and genome in aqueous humor. Am J Ophthalmol 138:46–54
42. de Visser L, Braakenburg A, Rothova A, de Boer JH (2008) Rubella virus-associated uveitis: clinical manifestations and visual prognosis. Am J Ophthalmol 146:292–297
43. Birnbaum AD, Tessler HH, Schultz KL, Farber MD, Gao W, Lin P et al (2007) Epidemiologic relationship between Fuchs heterochromic iridocyclitis and the United States rubella vaccination program. Am J Ophthalmol 144:424–428
44. Chee SP, Bacsal K, Jap A, Se-Thoe SY, Cheng CL, Tan BH (2008) Clinical features of cytomegalovirus anterior uveitis in immunocompetent patients. Am J Ophthalmol 145:834–840
45. Babu K, Adiga M, Govekar SR, Kumar BR, Murthy KR (2013) Associations of Fuchs heterochromic iridocyclitis in a South Indian patient population. J Ophthalmic Inflamm Infect 15:3–14
46. Bloch-Michel E, Dussaix E, Cerqueti P, Patarin D (1987) Possible role of cytomegalovirus infection in the etiology of the Posner-Schlossman syndrome. Int Ophthalmol 11:95–96
47. Sobolewska B, Deuter C, Doycheva D, Zierhut M (2014) Long-term oral therapy with valganciclovir in patients with Posner-Schlossman syndrome. Graefes Arch Clin Exp Ophthalmol 252:117–124

48. Accorinti M, Gilardi M, Pirraglia MP, Amorelli GM, Nardella C, Abicca I et al (2014) Cytomegalovirus anterior uveitis: long-term follow-up of immunocompetent patients. Graefes Arch Clin Exp Ophthalmol 252:1817–1824
49. Anninger WV, Lomeo MD, Dingle J, Epstein AD, Lubow M (2003) West Nile virus-associated optic neuritis and chorioretinitis. Am J Ophthalmol 136:1183–1185
50. Ng AW, Teoh SC (2015) Dengue eye disease. Surv Ophthalmol 60:106–114
51. Shantha JG, Yeh S, Nguyen QD (2016) Ebola virus disease and the eye. Curr Opin Ophthalmol. 27:538–544
52. Furtado JM, Espósito DL, Klein TM, Teixeira-Pinto T, da Fonseca BA (2016). Uveitis Associated with Zika Virus Infection. N Engl J Med. 375:394–6