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Leptospirosis in Switzerland: an emerging disease or emerging awareness?

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**UNIVERSITÉ
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**UNIVERSITÉ
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FACULTÉ DE MÉDECINE

Hôpitaux Universitaires de Genève
Section de médecine clinique
Département APSI (Anesthésiologie,
Pharmacologie, Soins Intensifs)
Service des Soins Intensifs

Thèse préparée sous la direction du Professeur Jérôme Pugin

**«LEPTOSPIROSE EN SUISSE:
Émergence d'une maladie ou prise de conscience ?»**

Thèse

présentée à la Faculté de Médecine
de l'Université de Genève
pour obtenir le grade de Docteur en médecine
par

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de

Troinex (GE), Dürrenroth (BE)

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I. RÉSUMÉ ET INTRODUCTION EN FRANÇAIS

1. INTRODUCTION

1.1. Epidémiologie et contexte géographique

Au niveau mondial

Au niveau mondial, la leptospirose est reconnue comme une zoonose en voie d'émergence et un problème de santé publique, en particulier dans les pays en voie de développement. Elle s'exprime par un état fébrile aigu et partage de nombreux symptômes peu spécifiques avec d'autres maladies comme la malaria, la dengue ou la grippe. La leptospirose pourrait représenter jusqu'à 20% des infections fébriles d'origine indéterminée, et son diagnostic est rendu difficile par la présence de plus de 250 serovariants de leptospires. De plus, la dynamique de transmission de cette infection bactérienne reste encore peu connue.

L'OMS estime une incidence annuelle globale à hauteur de 1.03 million de cas humains dont 58.900 décès et 2.90 millions de « Disability Adjusted Life Years » (DALYs) (=L'espérance de vie corrigée de l'incapacité (EVCI)). En Amérique elle se positionne au troisième rang des maladies infectieuses à risques, après la dengue et la grippe. L'incidence annuelle est estimée à 95,5 par 100'000 habitants en Afrique, 66.6 dans le pacifique occidental, 4.8 en Asie du Sud-Est et 0.5 en Europe.

De par son potentiel épidémique lié aux catastrophes naturelles (en particulier les inondations), son large impact économique autant sur les humains que les animaux et l'absence de stratégies de contrôle, de prise de conscience politique et de budgets à disposition pour des programmes de prévention et prise en charge de la maladie, la leptospirose porte le statut de « maladie négligée », « épidémie silencieuse » ou encore « menace sanitaire non reconnue ».

Pour parer à cette menace internationale, un groupement multidisciplinaire d'experts internationaux a vu le jour en 2011 sous la forme d'un réseau appelé « GLEAN: Global Leptospirosis Environmental Action Network ». Son but est de développer non seulement une prise de conscience de la maladie, mais aussi de nouveaux outils diagnostiques, de prévention et de contrôle de la leptospirose dans les populations à risques.

En Europe

En Europe, l'incidence de la leptospirose est estimée à 0.1-1/100'000 habitants dans les régions tempérées, avec une incidence de 0.13/100'000 habitants déclarés par l'ECDC en Europe en 2012. En France métropolitaine, le Centre National de Référence de la Leptospirose - Institut Pasteur - surveille activement cette maladie et indique un taux d'incidence de 0.4-0.5/100'000 habitants. En 2014 une augmentation des cas de 50% fut observée menant à un pic d'incidence à 0.98/100'000 habitants en France. La même observation fut faite aux Pays-Bas avec un nombre de cas autochtones 4.6 fois plus élevé en 2014 comparé à la moyenne surveillée en 2010-2013.

En Suisse

La leptospirose fut une maladie à déclaration obligatoire en Suisse jusqu'en 1998. L'incidence variait alors entre 2 et 13 cas reportés par année, soit une incidence moyenne de 0.05/100'000 -0.08/100'000 habitants jusqu'en 1998. Les données épidémiologiques font défaut après 1998 en raison de l'absence de système de surveillance nationale ou de déclaration obligatoire.

1.2. Introduction à notre étude

Dans un contexte d'émergence de la leptospirose au niveau mondial, avec des pics d'incidence observés dans des pays européens en 2014 et devant l'absence de données épidémiologiques en Suisse après 1998, cette étude a vu le jour dans le but d'évaluer la présence de la leptospirose en Suisse. Pour ce faire, nous avons interrogés en octobre 2014 des infectiologues dans tout le pays.

De plus, de par la répartition topographique particulière de la Suisse comportant autant des régions lacustres et citadines que des régions rurales de haute montagne, nous nous sommes intéressés particulièrement à l'impact du froid et de l'altitude sur le risque d'exposition et d'infection avec des leptospires. Nous avons ainsi parcouru la littérature à la recherche d'études effectuées dans des contextes géographiques ou climatiques similaires.

La leptospirose étant une zoonose, nous avons profité des connaissances approfondies de nos collègues vétérinaires à Berne avec qui nous avons collaboré tout au long de cette étude. Les données échangées avec les spécialistes du « Fish and Wildlife Institute » et du « Swiss Veterinary Reference Laboratory for Leptospirosis » afin de pouvoir estimer les risques environnementaux liés à cette maladie, a placé notre étude dans une lignée « One Health ».

Au moment où des groupes européens et internationaux se mettent en place pour réagir à une menace planétaire liée à la leptospirose, visant à mieux comprendre cette maladie, sa transmission, son impact sur les humains, les animaux et l'environnement, la question de la prise de conscience de cette maladie en Suisse s'est imposée naturellement.

Même si cette étude ne parvient pas à atteindre un seuil statistique significatif, notamment en raison de la difficulté de recruter des cas, elle permet néanmoins d'éclaircir nos connaissances au sujet de cette maladie qui est également présente en Suisse. En observant les données collectées localement et en les comparant avec celles d'autres pays européens d'une part, puis en comparant les symptômes et évolutions cliniques des cas suisses avec ceux des pays tropicaux où l'incidence de l'infection est très élevée d'autre part, nous sommes parvenus à dresser un tableau non exhaustif, mais néanmoins informatif de la réalité de cette maladie en Suisse. Ces informations juxtaposées aux données récoltées par les études vétérinaires donnent également du poids à nos résultats.

Au final, cette étude ne vise pas seulement à dresser une liste des cas de leptospirose acquis en Suisse et à établir une carte de sa répartition, mais invite à aussi à prendre conscience que cette maladie existe, qu'elle peut être présente dans des territoires variés, et que certaines populations à risques peuvent être exposées à une infection dont la morbidité et mortalité méritent certainement l'attention du corps médical voire de la santé publique.

1.3. Caractéristiques de la maladie et mode de transmission

Les leptospires sont des spirochètes gram-négatifs, classés en deux espèces: *Leptospira interrogans*, pathogénique pour les humains et de nombreuses espèces animales, et *Leptospira biflexa*, non pathogénique. La classification de *Leptospira interrogans* est subdivisée en sérovars (en fonction des spécificités antigéniques) et en sérogroupes basés sur des antigènes communs. Il existe plus de 200 sérovars et 12 sérogroupes pathogéniques.

Les spirochètes infectent l'organisme en pénétrant par les muqueuses des yeux, de la bouche, du nez ou des organes génitaux. Chez les humains, la contamination peut avoir lieu à travers les muqueuses ou des dermatabrasions ou coupures. Ou encore en contact avec des urines d'un animal infecté, de l'eau contaminée ou des sols humides contaminés.

Certains animaux, appelés « hôtes », peuvent héberger des leptospires dans leurs tubules rénaux sans succomber à la maladie (porteurs asymptomatiques). Ils servent ainsi de « réservoirs », permettant au pathogène de survivre dans ces animaux et être ensuite excrété dans l'environnement. Ce phénomène touche autant les animaux domestiques que les animaux sauvages.

Ce sont en premier lieu les petits mammifères et rongeurs qui sont « porteurs sains » de la maladie et la transmettent aux animaux de la ferme, les chiens, les humains ou dans l'environnement. Mais d'autres animaux domestiques ou sauvages peuvent également jouer le rôle de « réservoirs ».

La période d'incubation chez l'humain est en moyenne de 7-12 jours. Mais celle-ci peut s'étendre à 2-30 jours ce qui rend la localisation exacte de l'infection parfois difficile.

Les manifestations cliniques apparaissent typiquement en mode biphasique. La première phase correspond à la bactériémie, et s'exprime par des symptômes similaires à la grippe: fièvre d'apparition brutale, céphalées, douleurs abdominales et musculaires. La seconde phase dite « phase immunologiques » apparaît 2-3 ou 4 semaines après les symptômes initiaux et correspond à la production des anticorps. Ainsi, après une période de rémission, les patients observent une réapparition de la fièvre, léthargie, frissons et parfois des céphalées sévères (atteinte neuroméningée).

Le spectre de la symptomatologie peut être large. Certains patients restent asymptomatiques. D'autres développent une éruption cutanée, une suffusion conjonctivale, de la toux.

La forme la plus sévère de la maladie, dite « maladie de Weil », touche environ 5-10 % des cas. L'évolution clinique implique alors une insuffisance rénale et hépatique, une pancytopenie avec thrombocytopénie sévère qui peut mener à des hémorragies fatales. Les poumons peuvent également être touchés, ce qui s'exprime par de la toux, dyspnée, hémoptysie voir un syndrome de détresse respiratoire aiguë. Des symptômes cardiaques peuvent également être observés chez ces patients qui requièrent des soins intensifs aigus.

1.4. Outils diagnostiques

Les spirochètes sont très fragiles et rapidement détruits dans le sang et l'urine prélevés. De plus, mis en culture, ils ne poussent que très lentement ce qui rend le diagnostic de leptospirose difficile.

Dans les sept premiers jours post-exposition, au cours de la bactériémie, on utilise volontiers la PCR sanguine. Durant la deuxième semaine on préférera la PCR urinaire. Néanmoins, si la spécificité de la PCR sanguine et urinaire est bonne, sa sensibilité comme évoqué ci-dessus ne l'est pas et il faut s'attendre à des faux-négatifs.

Le test de référence pour le diagnostic de la leptospirose est le « MAT: test de microagglutination ». Sa spécificité est de 97%, la sensibilité varie de 30-76% en fonction du moment où l'échantillon a été prélevé. Typiquement, le test devient réactif après 3-

4 semaines et suit la production d'antigènes. Le MAT est essentiel pour toute étude épidémiologique car il permet d'identifier le sérovar de l'agent infectieux.

Quoi qu'il en soit, le diagnostic de leptospirose reste difficile et incertain car aucun de ces tests ne démontre une bonne sensibilité. Ainsi, le clinicien s'appuiera autant sur l'anamnèse, l'examen physique et les tests de laboratoires que sur ses connaissances de la maladie, afin de reconnaître les signes cliniques à temps pour initier au plus vite le traitement de choix.

1.5. Traitement

Le traitement doit être débuté le plus vite possible afin de prévenir les complications de la maladie. La doxycycline (100mg 2x/jour) ou l'azitromycine (500mg 1x/j) p.o. est recommandée pour les cas simples. Chez les enfants et les femmes enceintes on préférera l'azithromycine ou l'amoxicilline.

Pour les cas sévères, les recommandations mentionnent la pénicilline IV (1,5 million d'unités IV 4x/j), l'ampicilline (0.5-1g IV 4x/j), ceftriaxone (1g IV 1x/j) ou cefotaxime (1g IV 4x/j). Une admission aux soins intensifs s'avère nécessaire dans les cas graves qui développent un ictère et une insuffisance rénale aiguë oligurique et/ou un syndrome hémorragique. Le traitement sera spécifique à chaque complication (dialyse, ventilation mécanique, transfusion de plasma frais congelé et concentrés globulaires, drogues vasoactives etc.).

Une réaction de Jarish-Herxheimer peut se développer suite à l'administration de betalactamines (lyse bactérienne entraînant un syndrome inflammatoire aigu).

On évite cet effet secondaire avec l'administration de doxycycline dont les propriétés sont cytostatiques.

1.6. Prévention

Les mesures préventives s'appliquent autant de manière « collective » qu'individuelle.

Au niveau collectif, il s'agit en premier lieu de contrôler les réservoirs animaux en particulier les rongeurs. Une bonne gestion des inondations lors de catastrophe naturelles est essentielle, car les leptospires peuvent survivre longtemps dans les eaux contaminées par des animaux porteurs et exposer ainsi les populations touchées par les inondations.

Au niveau individuel, la prévention s'adresse aux professionnels exposés: agriculteurs, pisciculteurs, jardiniers, égoutiers, employés d'abattoirs. Ceux-ci peuvent se protéger des eaux souillées ou d'un contact direct avec les rongeurs en portant des gants, lunettes et bottes de protection.

Les sportifs pratiquant des loisirs en eau douce, que ce soit des baignades en rivière, lacs, étangs, sports nautiques (canoe-kayak, rafting, canyoning, pêche) ou encore le triathlon sont également à risque d'infection par les leptospires, en particulier en saison chaude et humides. Les chasseurs peuvent également être touchés. Informer ces populations à risques est primordial.

Il existe un vaccin spécifiquement dirigé contre le serovar *Leptospira icterohaemorrhagiae* (SPIROLEPT®) disponible en France et destiné à protéger les professionnels à risque (en particulier les éboueurs et égoutiers). Il n'est pas disponible en Suisse.

2. MÉTHODE

2.1. Plan d'étude

Le but de notre étude est d'évaluer la prise de conscience de la leptospirose en Suisse, de quantifier le nombre de cas diagnostiqués ces dernières années et d'établir une carte des cas collectés. Comme il s'agit d'une maladie rare, nous nous attendions à trouver peu, voire même aucun cas. De ce fait, une prévalence ou incidence fiable ne peut être mesurée. Il s'agit donc plutôt de présenter une première approche globale de la situation, en fonction des cas collectés.

Afin de parvenir à ce but nous avons utilisé plusieurs modèles de recherche. L'étude a débuté en août 2014 et s'est déroulée jusqu'en août 2016.

2.2. Revue de la littérature

Le premier modèle utilisé est une recherche de la littérature en vue de découvrir des études faites précédemment sur les sujet et de collecter des cas publiés en Suisse.

Nous avons étudié les articles en anglais, français et allemand trouvés à partir de Google ou Pubmed. Les mots-clés suivants ont été utilisés: leptospirose; leptospirose humaine; Suisse; altitude; montagne; froid; « one health »; OMS; CDC Atlanta; CDC Stockholm; Europe; France; Allemagne; Italie; Liechtenstein; Autriche; Pays-Bas; arctique; Nepal.

Notre intérêt a porté sur quatre points principaux:

- 1) Articles concernant les cas de leptospirose humaine diagnostiqués en Suisse. Nous avons collectés tous les cas publiés, sans limite de temps.
- 2) Articles concernant les cas de leptospirose animale en Suisse
- 3) Articles concernant les cas de leptospirose humaine en Europe
- 4) Articles concernant la leptospirose dans le monde entier avec une attention particulière aux régions froides ou en altitude (par ex. Nepal, US (Rocky Mountains) ou Russie)

2.3. Collection de données

Notre deuxième modèle d'étude se présente sous forme de collecte de données primaires ou secondaires.

La collecte de données primaire s'est faite en adressant un questionnaire à des infectiologues en Suisse en octobre 2014. Il s'agissait de déterminer si des cas de leptospirose avaient été diagnostiqués en Suisse ces dernières années et, si oui, de déterminer leur localisation. De plus, à travers un contact email ou téléphonique avec les infectiologues ayant reporté des cas, des informations complémentaires sur les symptômes, l'évolution clinique, l'âge, le sexe, les méthodes diagnostiques utilisées et le traitement de ces patients, ont pu être collectés et analysés.

Au-delà du questionnaire, nous avons eu des échanges avec des collègues de différentes branches scientifiques: des médecins, des vétérinaires, des spécialistes en laboratoire en France, aux Pays-Bas, du CDC Atlanta etc. Cela a permis une meilleure compréhension globale de la maladie.

Ensuite, à travers une collecte de données secondaires, nous avons pu enregistrer les cas de leptospirose reportés à l'office fédéral de la santé publique de 1989 à 1999.

Nous avons complété ces informations par la collecte du nombre de cas hospitalisés à partir de 1998 auprès de l'Office fédéral de la statistique.

2.4. Définitions cliniques

Tous les cas de leptospirose diagnostiqués en Suisse jusqu'en décembre 2015 ont été enregistrés dans l'étude. Ces cas ont ensuite été classifiés en cas « confirmés » et « cas probables » et en cas « autochtones » et « cas importés ».

3. RÉSULTATS

3.1. Revue de la littérature

Notre revue de la littérature s'est concentrée sur les thèmes suivants: leptospirose humaine et vétérinaire en Suisse, leptospirose en Europe et leptospirose au niveau planétaire, avec une attention particulière aux régions froides ou en altitude.

3.1.1. Leptospirose humaine en Suisse

La littérature suisse nous a permis de récolter 17 (53%) de 32 cas autochtones collectés au total, contribuant ainsi de manière importante à notre connaissance de la maladie en Suisse. Ces cas ont été publiés à Genève, Lausanne, Zürich, Lucerne, Bâle et au Tessin.

Le premier article date de 1984, le dernier de 2015. Toutes les informations épidémiologiques récoltées dans ces articles ont été introduites dans note base de données et figurent dans les Annexes 2a et 2b. Nous les décrivons plus en détails dans les chapitres suivants.

3.1.2. Leptospirose animale en Suisse

La leptospirose est une maladie bien connue des vétérinaires, et la revue de la littérature suisse a permis de mettre en exergue la présence de leptospirose parmi les chiens en Suisse, avec une augmentation nette des cas canins entre 2003 et 2012 (pic d'incidence en 2012 selon un article publié par la faculté VetSuisse à l'Université de Bern).

Un rapport du centre de médecine des poissons et animaux sauvages (FIWI) à Berne de 2015 montre une incidence stable parmi les castors, petits mammifères, renards et sangliers en Suisse. Une prévalence de *leptospira* spp. de 12,6 % parmi les petits rongeurs de la ville de Zürich est décrite dans un autre article. Une étude menée entre 2006 et 2008 a montré une séroprévalence de 58.5% parmi les chevaux sains. Finalement, le plus surprenant est un article décrivant une séroprévalence de 7.9% parmi les bouquetins testés entre 2008 et 2010.

3.1.3. Leptospirose en Europe

L'incidence de leptospirose est évaluée de manière très précise en France par le Centre National de Référence de la leptospirose à l'institut Pasteur à Paris. Ces dernières années, l'incidence aurait doublé en France avec un taux à 0.98/100'000 habitants en France métropolitaine en 2014. Les Pays-Bas surveillent également la maladie et ont observés une forte augmentation des cas humains et canins en 2014 alarmant les autorités de la santé publique.

En Allemagne, une étude publiée en 2005 investiguant des cas entre 1962 et 2003 décrit également une augmentation du nombre de cas entre 1998 et 2003. Entre 1997 et 2000, parmi 126 cas reportés, 10 sont décédés soit de défaillance multiviscérale, d'hémorragie pulmonaire ou cérébrale, de défaillance cardiaque ou syndrome de détresse respiratoire aiguë.

Le rapport de 2014 de l'ECDC à Stockholm concernant la période de 2008-2012 affirme que la leptospirose demeure une maladie rare en Europe. 10 décès ont été reportés.

Les groupes à risque seraient les agriculteurs et les personnes pratiquant les sports aquatiques.

En Italie, les cas ont majoritairement été reportés dans le nord du pays, principalement chez les hommes (88.9 %), dont la majorité (95.1 % des cas) vivait dans des régions rurales ou exerçaient des activités « à risques ».

En Autriche, une séropositivité de 10% fut trouvée en 2000 parmi les chasseurs comparé à un groupe contrôle (0%).

3.1.4. Leptospirose dans le monde: attention particulière aux régions froides et en altitude

Des études menées dans différentes régions du monde (US, Samoa, Nepal, Italie du Nord, Russie) démontrent que la maladie peut être présente en altitude et au-delà du cercle polaire. Une étude de laboratoire démontra même que des souches bactériennes de *Leptospira* spp. *Icterohaemorrhagiae* survécurent en moyenne 130 jours à 4 °C et gardèrent leur virulence malgré un environnement défavorable à pH < 6.

3.2. Résultats du questionnaire et autres sources d'information

Parmi 178 questionnaires envoyés aux infectiologues en Suisse en octobre 2014, 28 (16%) ont répondu, nous signalant soit des « cas » soit des « non-cas ».

D'autres informations nous sont parvenues directement de collègues infectiologues, internistes ou intensivistes, ou encore en communiquant directement avec des laboratoires.

C'est ainsi que notre base de données débutée avec la revue de littérature atteint au total 31 cas autochtones, la liste de cas importés 10 cas (lieu d'infection: Europe, Asie, Amérique centrale) et la liste des « non-cas suisses » 20 données (*voir pages 33 et 34 « Tables 1 et 2 » dans la version anglaise*).

Les informations collectées au sujet des cas autochtones ont permis l'élaboration de deux tables: l'une se concentre sur les informations liées aux patients et au diagnostic de la maladie (âge, sexe, lieu et date de l'infection, méthodes diagnostiques etc) et sont détaillées dans l'Annexe 3a, l'autre se concentre plutôt sur les symptômes et l'évolution clinique de la maladie dans l'Annexe 3b.

Nous allons analyser ces tables de manière plus précise dans les chapitres suivants.

3.3. Epidémiologie descriptive des cas autochtones infectés de 1970 à 2015

Informations générales

L'âge de nos patients se situe entre 25 et 88 ans, avec un âge moyen de 50.8 ans. Aucun cas d'infection pédiatrique autochtone ne nous est reporté. Parmi les 31 patients, 20 sont des hommes (65%) et 6 des femmes (19%). Dans 5 cas le sexe n'est pas connu. 3 patients ont été traités en ambulatoires et il est probable, sur la base des données cliniques, que les autres 28 patients aient été hospitalisés.

Parmi nos 31 cas, 21 cas ont été confirmés par PCR ou sérologie.

Signes et symptômes cliniques, résultats de laboratoires et complications

Des informations sur les signes et symptômes cliniques nous sont parvenues pour 22 patients. Parmi eux, 80% présentent de la fièvre ainsi que des myalgies, arthralgies et malaise. Des céphalées sont mentionnées dans 45% des cas, certains présentent des signes méningés. Des symptômes digestifs (douleur abdominale ou épigastrique, nausée, vomissement ou diarrhées) apparaissent dans 27% des cas. De la toux, dyspnée, conjonctivite et pétéchies sont observés chez d'autres. Un ictère est présent dans 23% des cas (*voir graphique page 36 de la version anglaise*).

Parmi les résultats de laboratoire, on note une perturbation des tests hépatiques dans 46% et une atteinte rénale dans 67% des cas. 42% des patients présentent une thrombocytopenie ou pancytopenie. Des troubles de la coagulation ont mené à une hémorragie massive pulmonaire chez une patiente et une hémorragie cérébrale suivie de décès chez un autre patient.

13% des patients ont montré une atteinte cardiaque (arythmie ou myocardite). Un patient a été traité 45 jours aux soins intensifs pour une défaillance multiviscérale. Il a survécu, ce qui n'est pas le cas de 2 de nos 31 patients, soit un taux de mortalité de 6 %.

3.4. Evaluation de la localisation, de l'exposition et de groupement de cas

En localisant le lieu d'infection de nos 31 patients, nous avons établi une carte de la répartition des cas en Suisse (*voir figure 5, page 39 de la version anglaise*).

Quatre regroupements de cas ont été observés. Le premier groupement se situe à Genève parmi les pêcheurs: 3 des 15 pêcheurs professionnels sur le territoire genevois ont été infectés entre 2008 et 2013. A Bremgarten, dans le canton d'Argovie, 3 surfeurs ont contracté la maladie sur la rivière Reuss. Ces cas ont été diagnostiqués et publiés à Zürich (Triemli Spital). Un troisième regroupement de cas a été observé dans le Val Müstair, une région montagneuse au sud-ouest de la Suisse en 2013. Enfin, un article décrit 4 cas d'infection de leptospirose après une baignade dans un lac au Tessin au début des années 1970.

Ainsi dans 3 des 4 regroupements de cas, l'infection est liée à une activité aquatique (pêche, surf sur une rivière et baignade).

Parmi nos 31 patients inclus dans cette analyse, 6 autres pratiquaient une activité reliée à l'eau au moment de l'infection, ceci représentant ainsi un facteur de risque principal (16 sur 27 (60%) cas).

Un autre facteur de risque observé est le contact direct ou indirect avec des rongeurs.

3.5. Office fédéral de la santé publique et office fédéral de la statistique

L'office fédéral de la santé publique a enregistré une incidence de 0.08/100'000 habitants entre 1989 et 19999 sur la base de déclarations provenant de médecins ou de

laboratoires. L'obligation de déclarer les cas de leptospirose humaine a été supprimée en 1999.

L'office fédéral de la statistique enregistre le diagnostic de tout patient hospitalisé en Suisse. Nous avons ainsi pu observer 71 cas d'hospitalisation avec un diagnostic de leptospirose entre 1999 et 2003. Cela représente en moyenne 4,73 cas /année, soit un taux d'incidence de 0,06 /100'000 habitants/année.

(voir figures 7 et 8, pages 41 et 42 de la version anglaise).

3.6. Médecine vétérinaire

En Suisse, l'institut de bactériologie animale (faculté VetSuisse à Berne) surveille la leptospirose chez les animaux domestiques. A ce jour aucune augmentation de cas n'a été observée chez les bovins, chevaux ou moutons.

Les animaux sauvages sont surveillés par le Centre de médecine des poissons et animaux sauvages à Berne (FIWI, faculté VetSuisse à Berne). Une étude a récemment observé l'évolution sérologique de la leptospirose au moyen de tests MAT parmi les castors, renards, sangliers et rongeurs. Si des animaux séropositifs sont trouvés dans tout le pays, y compris dans les régions montagneuses, l'incidence de la maladie semble stable dans ces populations.

Enfin, une étude démontre une croissance significative de cas de leptospirose canine depuis 2010. D'autres études sont encore en cours.

3.7. Approche « One Health »: exemple du Val Müstair

Dans ce chapitre nous décrivons 3 cas de leptospirose probable chez des habitants du Val Müstair, dans le sud-est des Alpes suisses. Les trois cas ont été diagnostiqués en mai 2013 et le médecin local s'est posé la question de savoir s'il devait craindre une épidémie. Afin de répondre à cette question, une approche « One Health » impliquant à la fois les infectiologues, biologistes, vétérinaires et gardes faunes locaux a été adoptée.

Le premier cas est un hôtelier de 60 ans, qui présente d'abord des symptômes grippaux, puis 10 jours plus tard un état fébrile aigu, accompagné de douleurs abdominales, vomissements, toux et sueurs nocturnes. A part une CRP à 212 le reste des examens de laboratoire, la radio du thorax et tous les examens complémentaires effectués (CT thoraco-abdominal, test immunologiques etc) étaient normaux. Un test sérologique ELISA posa le diagnostic de leptospirose et le patient fut traité avec la doxycycline. Aucun contact direct avec des rongeurs ni aucune activité à risque (chasse, pêche etc) ne fut pratiquée. Le patient vit en région rurale et aime les randonnées en montagne.

Le deuxième cas est une étudiante de 27 ans, vivant dans la même vallée. Elle se présente chez son médecin pour des céphalées intenses et une otalgie. Traitée initialement pour ce qui semblait être une otite, les céphalées persistent, accompagnées d'une diminution de concentration sans autre atteinte neurologique. L'IRM cérébrale et les examens de laboratoires sont tous normaux. Malgré cela, l'état subfébrile et la diminution de l'état général et les céphalées persistent. Au vu du résultat positif du premier cas de leptospirose, le médecin effectue également un test sérologique qui revient positif pour la leptospirose. La patiente est traitée avec la doxycycline et se rétablit rapidement. Il se peut que la patiente ait eu contact avec des excréments de souris ou de chauve-souris dans un grenier.

Le troisième cas est une patiente de 88 ans, très sportive (randonnées en montagnes) habitant également dans le val Müstair. Deux semaines après une bronchite dont elle s'est bien remise débutent un état fébrile aigu, une toux et des sueurs nocturnes. Le diagnostic de leptospirose est rapidement posé (sérologie ELISA) et le traitement de doxycycline instauré. Aucune séquelle n'est notée. Elle a un chat qui lui ramène occasionnellement des souris, mais elle n'a pas eu de contact direct avec les rongeurs.

Ces trois cas ont été diagnostiqués en mai 2013 dans cette vallée des Grisons située entre 1200 et 2000 mètres d'altitude. Le médecin-chef de l'hôpital local a pensé à la leptospirose de par son expérience en médecine tropicale. L'apparition biphasique des symptômes des patients lui paraissait typique de la maladie. Aucun autre cas n'a été noté ni précédemment ni depuis. Le médecin s'assura auprès de la faculté Vet-suisse à Berne qu'aucune épidémie de leptospirose animale (domestique ou sauvage) n'était observée à ce moment en Suisse, et dans cette région en particulier. Il s'informa auprès du garde faune qui lui expliqua qu'une épidémie de maladie de carré avait tué plusieurs prédateurs quelques années plus tôt, ce qui aurait pu mener à une augmentation de la population de rongeurs. Au moment du diagnostic les animaux sauvages étaient en bonne santé.

4. DISCUSSION

4.1. Evolution de la leptospirose en Suisse

L'évolution de la leptospirose peut être catégorisée en deux groupes: l'un « avant 1998 », soit la date à partir de laquelle la maladie ne doit plus obligatoirement être déclarée et « après 1998 ».

Sur la base des données de l'office fédéral de la santé publique de 1988 à 1998, l'incidence calculée à partir des 61 cas collectés ces 10 années est de 0,08/100'000 habitants.

Après 1998, aucune donnée officielle n'existe, et en l'absence de laboratoire de référence pour la leptospirose humaine en Suisse, les échantillons sont envoyés en Allemagne pour le diagnostic MAT. Sur la base de réponses à notre questionnaire nous avons cependant récolté des cas autochtones diagnostiqués après 1998. En intégrant les données de l'office fédéral de la santé publique « avant 1998 », les données de l'office de la statistique, les réponses à notre questionnaire et notre revue de la littérature nous sommes parvenus à un graphique de l'évolution des cas en Suisse de 1989 à 2014 (*voir figure 10 page 49 de la version anglaise*). Ce graphique montre une incidence moyenne de 5 cas/année qui semble stable à travers toute cette période de temps. Seuls les deux dernières années montrent un pic à 8 cas en 2013 et 11 cas en 2014.

Cela pourrait s'expliquer d'une part par le fait que dans notre questionnaire envoyé en 2014 nous avons récolté des cas traités en ambulatoire, avec des symptômes moins sévères que ceux probablement déclarés précédemment ou « seulement les cas hospitalisés » enregistrés par l'office de la statistique.

Ce graphique est donc à interpréter avec prudence. En effet, les cas sévères ne représentent qu'environ 10% des cas d'infection à la leptospirose. Orientant notre attention sur les cas hospitaliers seuls présente le risque de sous-estimer jusqu'à 90% des cas !

En plus du biais « patients traités en ambulatoire versus hospitalisés » il existe aussi le biais des cas « autochtones » ou « importés ». Il ne nous est pas possible de savoir si les patients hospitalisés et apparaissant dans les statistiques ont été infectés en Suisse ou à l'étranger.

Néanmoins, ce graphique nous permet une première approche de l'évolution de cette maladie peu connue en Suisse. L'augmentation des cas en 2013 et 2014 concerne avant tout des pratiquants de sports aquatiques. Au niveau mondial, cette source d'infection devient de plus en plus connue, notamment suivant des épidémies de leptospirose observés parmi des participants au triathlon et autres sports aquatiques dans l'Illinois (1998), en Floride (2005) et en Allemagne (2006).

4.2. Approche « One Health »: comparaison des résultats humains avec ceux de l'étude des animaux sauvages

L'interprétation de nos données, à elle seule, est difficile au vu du petit nombre de cas de leptospirose humaine en Suisse. Néanmoins, si nous comparons celle-ci avec les données récoltées par nos collègues vétérinaires, notre perception s'affine et devient plus précise.

Nous pourrions par exemple mettre en doute la possibilité d'infection humaine à la leptospirose en région montagneuse et fraîche, vu que cette maladie est plus connue en relation avec l'eau et les régions tropicales. De plus, les trois cas décrits sont des cas « probables » et non confirmés du fait qu'une seule sérologie, positive, a été effectuée.

Or si l'on s'intéresse à l'étude menée par la FIWI à Berne, nous apprenons qu'un renard séropositif a été dépisté dans le Val Müstair et un renard positif à la PCR dans une vallée avoisinante, prouvant que cette maladie peut bien être présente en altitude aussi. Ces chiffres sont similaires à ceux trouvés chez les renards dans d'autres régions suisses et montrent qu'une incidence similaire est trouvée chez ses animaux « sentinelles », indépendamment de la localisation géographique ou l'altitude.

Ainsi, cette étude vétérinaire augmente significativement la valeur « pré-test » de la sérologie pour la leptospirose dans ces régions montagneuses.

4.3. La Suisse au centre de l'Europe: comparaison de nos résultats avec ceux d'autres pays européens

Si en Suisse la leptospirose n'est plus une maladie à déclaration obligatoire depuis 1999, elle est observée de manière très précise en France et aux Pays-Bas en particulier. Ainsi, s'il ne nous est pas possible de comparer directement nos données avec celle de notre pays voisin, la France, nous pouvons néanmoins nous demander si l'augmentation de cas observés en France pourrait signaler également une augmentation de cas en Suisse.

De plus, les Pays-Bas ont constaté une augmentation parallèle des cas canins et humains. En Suisse, l'augmentation de cas canins a été constatée par les vétérinaires à Berne. Ainsi, l'hypothèse de l'augmentation de cas également en Suisse mérite d'être posée.

4.4. Série de cas particuliers: leptospirose en altitude dans le Val Müstair

Comme décrit précédemment, la probabilité que nos trois cas de leptospirose humaine en altitude dans le sud-est de la Suisse soient de vrais positifs est appuyée par

la présence de cas animaux dans la même région. De plus, une étude italienne montre que 83,3% des cas de leptospirose avaient été trouvés dans le Nord du pays. Une étude autrichienne montre que la chasse est un facteur de risque. Le Val Müstair est une région montagneuse à la frontière de l'Italie du Nord où la chasse est beaucoup pratiquée. La présence de séropositivité pour la leptospirose chez des bouquetins soutient l'hypothèse qu'une infection est tout à fait possible aussi dans des régions en altitude.

4.5. Enjeu de la sous-estimation potentielle d'une maladie « négligée »

L'OMS et le GLEAN (Global Leptospirosis Environmental Action Network) ainsi que de nombreux auteurs internationaux ont insisté sur le fait que la leptospirose est au niveau mondial une maladie « négligée » et très probablement sous-estimée. En effet, les symptômes peu spécifiques ou atypiques d'une part, des tests de laboratoires coûteux ou peu fiables de l'autre, rendent le diagnostic difficile. Le diagnostic différentiel d'un état « grippal » est large, et les symptômes de la leptospirose peuvent être interprétés comme une grippe, pneumonie, gastroentérite, ou dans les pays tropicaux: dengue, fièvre typhoïde ou malaria. Les formes sévères avec atteintes multiorganiques présentent néanmoins une morbidité élevée qui a elle seule mérite l'attention des professionnels de la santé publique, aussi en Suisse.

4.6. Conscience globale et facteurs favorisant la détection de cas humains

Au niveau mondial, le GLEAN crée en 2011 en collaboration avec l'OMS montre l'importance d'une prise en charge globale et « One Health » dans l'approche de la leptospirose. Leur but n'est pas seulement de développer des outils diagnostiques performants et peu coûteux, pouvant être rapidement utilisés en cas de catastrophes naturelles, mais aussi d'inviter les institutions internationales et politiques à prendre conscience de cette maladie.

En Europe, c'est le KIT (Royal Tropical Institute Amsterdam) qui a lancé une étude européenne sur le sujet.

En Suisse, plusieurs départements de la faculté Vetsuisse à Berne et Zürich mènent des études sur la leptospirose.

Au niveau de la médecine humaine en Suisse, la maladie reste peu connue. Elle est associée avant tout à la médecine tropicale. Les infectiologues et intensivistes l'associent le plus souvent à une atteinte rénale et hépatique (maladie de Weil) et la source d'infection la plus connue reste l'eau contaminée par des rongeurs.

Qu'en est-il de tous les autres cas présentant des symptômes moins spécifiques ? L'information sur la leptospirose commence à circuler parmi les pêcheurs professionnels genevois, et aussi parmi les surfeurs sur la Reuss. C'est ainsi que les patients eux-mêmes, ayant entendu parler de la maladie, ont prié leur médecin de tester la leptospirose, menant au « pic » de nombre de cas suisses en 2013 et 2014.

La présentation lors d'un congrès national en 2015 d'un poster sur les cas de leptospirose chez les surfeurs par les infectiologues zurichois est un premier pas vers une prise de conscience plus large sur les signes et symptômes mais aussi les facteurs de risque de cette maladie en Suisse.

5. CONCLUSION

5.1. Leptospirose en Suisse: une maladie potentiellement létale, probablement sous-estimée et sous-diagnostiquée, peut-être d'importance locale et globale

Dans cette étude nous avons analysé la présence et l'évolution de la leptospirose en Suisse, basée d'une part sur les déclarations obligatoires de l'office fédéral de la santé publique jusqu'en 1998, puis sur un questionnaire envoyé aux infectiologues suisses en 2014.

Si la leptospirose est une maladie rare qui n'est pas soumise à une déclaration obligatoire depuis 1998, cette étude montre qu'elle reste néanmoins endémique.

Loin des références habituelles associant le plus souvent cette maladie à une seule exposition tropicale, nous avons retrouvé des cas autant en bordure de lac à Genève qu'en zone rurale et alpine dans le sud-est des Alpes !

Ainsi, les leptospires peuvent non seulement survivre mais aussi infecter la population à des températures basses et en altitude.

Les signes et symptômes ainsi que l'évolution clinique de la maladie est similaire chez nos patients comparés aux cas importés des tropiques. Variant d'un « simple état grippal » à une défaillance multiorganique nécessitant des soins intensifs de longue durée, la morbidité et mortalité de cette maladie sont potentiellement sous-estimées en Suisse.

En effet, nos données indiquent environ 5 cas de leptospirose /année en Suisse, avec une incidence de à 0,08/100'000 habitants. En France voisine, l'incidence déjà bien supérieure à celle mesurée en Suisse a augmenté de 0.43/100'000 habitants à 0.98/100'000 habitants en 2014, selon le centre national de référence de la leptospirose à Paris. Une augmentation de l'exposition environnementale de cette zoonose pourrait également avoir eu lieu en Suisse comme le fait supposer une étude de la faculté Vetsuisse à Berne qui démontre l'augmentation des cas canins sur notre territoire.

Au niveau international comme en Suisse, les activités aquatiques (pêche, natation dans des lacs et rivières, voile et plongée) semblent être un facteur de risque. Dans notre étude les pêcheurs représentent 10% de nos 31 cas, les surfeurs 13%, natation dans des lacs ou rivière 16%. 19% des patients indiquent un contact direct avec des rongeurs, 19% avec des excréments de rongeurs et 10% se trouvaient en altitude ou en zone rurale.

Conscients que cette étude est basée sur un petit nombre de cas de leptospirose humaine acquise en Suisse et qu'ainsi aucune valeur statistiquement significative ne peut être atteinte, nous recommandons néanmoins de plus amples investigations scientifiques, notamment parmi des groupes à risques comme dans le milieu des sports aquatiques.

Une meilleure connaissance des voies de transmissions mais aussi des symptômes cliniques dans le milieu médical et dans les populations « à risques » permettraient un diagnostic et traitement plus rapides et d'éviter des complications sévères.

Au niveau international des groupes de recherche travaillent à l'élaboration de tests diagnostiques peu coûteux et plus sensibles que ceux existant sur le marché. En

Suisse, il serait souhaitable de regrouper les analyses dans un laboratoire de référence, comme il en existe un en France. Sur notre territoire, il existe un laboratoire de référence vétérinaire à la Faculté Vetsuisse à Berne. S'il existait un laboratoire de référence pour la médecine humaine, de plus amples études épidémiologiques sur la leptospirose humaine pourraient voir le jour.

Enfin, quand certains pays voisins et internationaux parlent de « maladie émergente », la question de la réintroduction de la déclaration obligatoire, voire d'un monitoring de la leptospirose pourrait être discutée en Suisse.

5.2. Outputs: « Recommandations »?

Nous recommandons aux autorités sanitaires suisses de porter attention à la leptospirose humaine en Suisse, car celle-ci pourrait, comme dans certains pays voisins et internationaux, être en augmentation.

Nous invitons le corps médical à suspecter une leptospirose chez tout patient fébrile ayant eu une activité à risque comme des sports aquatiques, un contact avec des rongeurs ou des excréments de rongeurs (typiquement de l'eau contaminée), ou encore vivant en région rurale. Les symptômes peu spécifiques comme un état grippal, des douleurs abdominales, toux et des céphalées intenses doivent, dans un contexte d'exposition à risque (période d'incubation jusqu'à 30 jours), faire penser à une leptospirose, et les examens complémentaires (PCR sanguine, urinaire, MAT) effectués rapidement afin d'instaurer le traitement approprié et d'éviter des complications sévères (10% des cas) comme une déviance multiorganique, coagulopathies et hémorragies massives.

Enfin, des études plus approfondies pourraient, s'il apparaît que la prévalence de leptospirose est plus élevée qu'attendue, permettre l'établissement de panneaux de prévention sur les lieux d'infection potentiels (bord de lac, rivières etc) ou d'information à la population.

L'installation d'un laboratoire de référence pour la leptospirose en Suisse permettrait de regrouper les cas diagnostiqués et, au moyen de MAT, de définir les sérogroupes impliqués et permettre un monitoring de la maladie en Suisse. Un vaccin contre le serogroupe *Icterohaemorrhagiae* est actuellement disponible en France. Son introduction en Suisse pourrait être rediscutée, notamment parmi les populations à risques.

6. REMERCIEMENTS

Voir la version anglaise

7. LISTE DES REFERENCES

Voir la version anglaise

II. THESIS

1. INTRODUCTION

1.1. Epidemiology and geographical background

Worldwide

Leptospirosis, to date known as a global “emerging” zoonosis [1, 2] [3-5], is a worldwide growing burden for public health, in particular in developing countries. It presents with acute undifferentiated fever and diverse common symptoms shared with other well-known diseases such as malaria, dengue [3], and influenza [1]. Furthermore, leptospirosis might represent up to 20% of febrile illnesses of unknown origin [6]. Transmission dynamics of this bacterial infection are still poorly understood, and laboratory confirmation is complex in the presence of more than 250 sero-variants of leptospire, thus rendering the diagnosis difficult [3].

The WHO estimates the annual global incidence to 1.03 million human cases with 58,900 deaths [7] and 2.90 million Disability Adjusted Life Years (DALYs) lost each year (*estimated by the Leptospirosis Burden Epidemiology Reference Group “LERG”, WHO*). It is one of the top ten infectious hazards reported globally in the Event Management System (EMS) and in the Americas, leptospirosis events were, after dengue and influenza, the top third infectious hazards in the EMS[8]. Annual incidence was estimated to be 95.5 per 100'000 population in African Region, in the Western Pacific 66.6, in the Americas 12.5, in South-East Asia 4.8, and in Europe 0.5 [6].

The epidemic potential linked to climate events (in particular flooding) and the high economic impact on human and animals combined with lacks in control strategies, political awareness and budget allocations for plans and programs gave leptospirosis, on an international level, the status of a “neglected disease”, a “silent epidemic disease” or an “unrecognized One Health threat”[3] [8, 9].

In a setting of global warming and heading an alarming challenge, efforts in an attempt to fight leptospirosis merged into the creation of the Global Leptospirosis Environmental Action Network (GLEAN) in 2011, which was developed by WHO and the Health and Climate Foundation. The aim of this initiative, based on the “One Health concept”, is to create a network of international multidisciplinary experts in order to improve knowledge, diagnostic tools, prevention and control of leptospirosis in high-risk populations [9].

Europe

In temperate countries incidence is estimated at 0,1-1/100'000 [5], with 0,13/100'000 reported in Europe by the ECDC in 2012 [10]. In Metropolitan France a higher incidence rate of 0,4-0,5/100'000 is noted by the national reference laboratory actively monitoring the disease [11]. An increase of up to 50% of annual cases was observed in 2014, thus showing an incidence of 0.98/100'000 in France in 2014 [12]. The Netherlands also actively monitor the disease and report an 4.6-fold increase in autochthonous cases in 2014 compared to the annual average in 2010-2013 [13].

Switzerland

In Switzerland the disease was notifiable until 1998, and incidence varied from 2 to 13 cases annually before 1998, with a mean incidence of 0,05/100'000 – 0.08/100'000

population[14, 15]. After 1998, the disease has not been notifiable any more, thus clear epidemiologic data have been lacking since then.

1.2. Introduction to our study

In order to cast light into the currently unclear situation we conducted a study to assess the presence of the disease in the country, asking infectious disease specialists in Switzerland about recent cases.

The specific topography of the country, ranging from cities bordering lakes and rivers to remote mountain valleys, further raised the question of the impact of cold and altitude exposures on the risk of infection, and a specific attention was brought to studies conducted in similar settings worldwide.

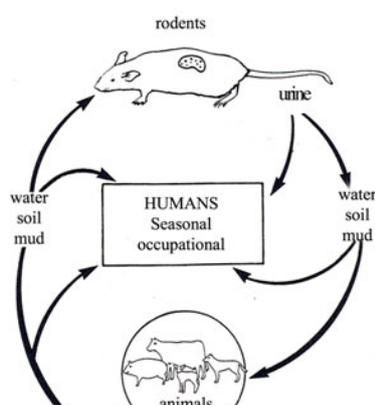
As Leptospirosis is a zoonosis, tight collaboration with veterinary specialists from the Fish and Wildlife Institute and the Swiss veterinary reference laboratory for Leptospirosis in Bern were essential in assessing environmental risks and settings, thus placing this study in a One Health perspective.

The question of awareness of the disease in Switzerland seems crucial at a time when European and international groups are being created in an attempt to better understand the disease, its transmission, its impact on humans, animals and economics. They are struggling to find rapid solutions for diagnosis and strategies for the prevention and the management of outbreaks.

The difficulty of enrolling a large group of patients precluded reaching sufficient statistical power. Yet, observing collected data and comparing them with those collected in other European countries, or comparing clinical evolutions with those from high-prevalence tropical countries support our findings in Switzerland. Furthermore, comparing our data with those collected by veterinarian colleagues further highlights our research on Leptospirosis in Switzerland.

1.3. Disease features and transmission

Leptospire are gram-negative, highly motile spirochetes classified in 2 species: *Leptospira interrogans*, pathogenic to humans and to a variety of animals, and *Leptospira biflexa*, a saprophytic and nonpathogenic organism. *Leptospira interrogans* itself is subclassified into serovars, according to antigenic differences, and into serogroups depending on common antigens [4]. To date, more than 200 serovars and 12 pathogenic serogroups have been identified. Infection occurs when the organism enters through mucous membranes of eye, mouth, nose or genital tract.



In humans, the most known infection pathway is through mucous membranes and cuts or dermabrasions [16]. Another route of infection is contact with infected urine of animals, or water or moist soil contaminated by urine of these animals, carrying the *leptospira* in their renal tubules without getting sick. These wild or domestic animals can serve as reservoirs for the disease. The pathogens can survive in these host animals and then be shed in the environment [4]. Small mammals are considered to be the most important maintenance hosts by transferring the infection to domestic farm animals, dogs and humans [1].

Figure 1 Cycle of leptospirosis transmission [17]

But almost every species of rodent, marsupial and mammal could carry and excrete leptospire [2, 17].

For humans, average incubation period is 7-12 days, but can vary as much as from 2-30 days, rendering the exact moment or location of infection sometimes difficult to find [4].

Clinical features

Clinical features of leptospirosis are very diverse, rendering its diagnosis difficult.

An early phase resembling a common flu with sudden onset of fever, headaches, myalgia and abdominal pain typically occurs, corresponding to the bacteremia.

A second phase, following a short time of recovery, then follows, with reappearance of symptoms with fatigue, fever, chills and sometimes severe headaches. This phase corresponds to the «immunologic phase», when the rise in antibody titers occurs, typically in week 2-3 or 4.

Sometimes, other signs and symptoms such as rash and conjunctival effusion occur, or cough, and in some patients a completely asymptomatic course has been observed [18].

A more severe form of leptospirosis called “Weil Disease”, accounting for about 5-10% of cases, evolves into rapid liver and kidney failure, and pancytopenia with severe thrombocytopenia can lead to fatal hemorrhages. Pulmonary symptoms range from cough, dyspnea and hemoptysis to adult respiratory distress syndrome and can cause death [1]. These patients often need intensive care unit support and dialysis. Cardiac involvement is also a common, maybe underestimated feature [1].

Another form of leptospirosis called “aseptic meningitis” has been observed, and typically occur in younger patients and women [1].

Some infections are complicated by a “post-leptospirosis syndrome”[16], including fatigue, malaise, myalgia and headaches lasting up to 24 months.

1.4. Diagnostics

Diagnosing leptospirosis can be very difficult. This Spirochetes is very sensitive and is rapidly destroyed in blood or urine.

A helpful test if Leptospirosis is suspected in the early phase up to 7 days is the PCR in blood. PCR in urine can start to be performed in the second week, can however be negative because of intermitted shedding of pathogen in the urine. Both tests, PCR in blood and in urine can be falsely negative, but specificity is very high. The limitation of PCR is the inability to identify the infecting serovar, which does not affect the individual treatment of patients, but is of significant epidemiologic value [1].

The standard test remains serology (typically with ELISA), expected to be negative if tested too early, a rise in titers is diagnostic in the following 2-4 weeks after the beginning of the symptoms. To confirm a case, 2 serology test with a significant rise in titers need to be observed.

Eventually, the MAT (microagglutination test) is the gold standard for a diagnosis of leptospirosis [19]. Its specificity is 97% and sensitivity between 30-76%, depending on the time of testing (it may take up to 3 or 4 weeks to become reactive) [20, 21]. It gives

also helpful information on the type of leptospirosis infection by revealing the serovar of the infecting *Leptospira* spp, which is not essential for the clinical diagnosis, but is crucial for any epidemiologic study.

Culture is seldom accomplished, since growth of the bacteria is very low and the test little sensitive.

Neither of these tests have shown a good sensitivity, and a combination of history, physical examination, laboratory results and knowledge of the disease is essential if a clinical diagnosis and appropriate treatments ought to be initiated as soon as possible.

1.5. Treatment

Treatment should be initiated as soon as possible in order to prevent severe to fatal complications. In milder forms, doxycycline (100mg 2x/day) or azithromycin 500mg 1x/day in oral treatment are recommended. In children or pregnant women, azithromycin or amoxicillin should be given adjusted to weight.

In more severe forms, IV penicillin (1,5 million unit IV every 6h), ampicillin (0.5-1g IV every 6h, ceftriaxone (1g IV every 24h) or cefotaxime (1g IV every 6h) are recommended. In cases where hospitalization is not possible, ceftriaxone once daily can be given intramuscularly [22].

In the severe forms intensive care unit support including dialysis, respiratory and vasoactive drug support, FFP or transfusion may be needed [23].

Note that the initiation of B-Lactamase treatment can lead to Jarish-Herxheimer reaction which can mimic a septic choc [24]. Doxycycline, due to its cytostatic properties (vs. cytolytic in B-Lactamase) prevents this adverse effect of antibiotic therapy.

1.6. Prevention

Prevention of leptospirosis concerns collective and individual measures. On a collective level, control of rodent population and management of flooded areas are primordial [22].

On an individual level, information should be given to the “at-risk” population such as farmers, breeders, sewage workers and fish breeders. Direct manipulation of rodents or contact with water infested by rodents should be protected with gloves and glasses and boots [16].

Other activities at risk are outdoor sports connected with water such as fishing, rafting, canoeing or kayak and swimming in rivers and lakes, and hunting [11, 25]. Triathlon has been a source of leptospirosis outbreaks in different countries [26-31]. Cleaning and disinfection of wounds and protection with waterproof dressings are recommended.

Eventually, the vaccine for the form “*icterohaemorrhagiae*” is available in France and can be obtained on special request [32]. It is called “Spirolept” and its efficacy in preventing infection from other leptospirosis serovars is not proven yet, thus its use is not recommended to date in Switzerland by the Ministry of Public Health [33]. Its indication could be discussed for specific “at-risk activities”, especially in tropical countries.

2. METHODOLOGY

2.1. Study design

The aim of our study is to cast light on the actual awareness of disease in Switzerland, to quantify diagnosed cases in the past years, and to establish a map of collected cases. As leptospirosis is a very rare disease, a very small number of cases, if any at all, was expected to be collected. Thus, a reliable prevalence or incidence was not expected to be measured, but rather an estimation or a first approach towards what has been assessed recently or in the past. In order to achieve this goal a combination of study designs was applied and conducted from August 2014 until August 2016.

First a literature review was conducted in order to collect information on previous studies and published case-reports in Switzerland. Second, a primary data collection was done by a questionnaire that was sent to infectious disease specialists in the country in September 2014; this aimed at collecting new cases or cases that have not been published yet. Third, a secondary data research was done based on the analysis of recorded data by the Federal Office of Public Health and the Federal Office of Statistics. Fourth, case-series will be described, and even though inferences cannot be generated for the general population based on the current study, still hypotheses on causal factors or the “at-risk” environment can be proposed. Fifth, with the help of an analytical observation and a descriptive study of the patient’s history and disease features, routes of infection and geographical settings, the pertinence of further assessment of the disease in Switzerland and a possible impact of the disease in particular patient groups or on a public health level can be discussed. Eventually, a tight collaboration with the veterinary institutes places this research in a One Health approach, where environmental and veterinary data support the assessment of human leptospirosis evolution in Switzerland.

2.2. Literature review

Articles in English, French and German were found through electronic resources like Google and Pubmed and by scanning reference lists of relevant articles.

The following keywords were used: leptospirosis; human leptospirosis; Switzerland; altitude; mountain; cold; One health; WHO; CDC Atlanta; CDC Stockholm; Europe; France; Germany; Italy; Lichtenstein; Austria; Netherland; Arctic; Nepal.

A further focus was set on four main categories:

- 1) Articles concerning human leptospirosis cases diagnosed in Switzerland. No time limit was set, and all articles published on that topic were collected, including locally acquired as well as imported cases of leptospirosis.
- 2) Articles concerning animal leptospirosis in Switzerland
- 3) Articles concerning human leptospirosis in Europe (in particular direct neighbouring countries like France, Germany, Lichtenstein, Austria and Italy), aiming at getting a better spatial overview of the disease and comparing these results with the Swiss results. The Netherlands hold a national reference center for leptospirosis and it is a notifiable disease; these data are thus a reliable source of information and comparison and are discussed in this study. Reports from the ECDC (European Center of Disease Control) have been used for comparative purposes as well.

- 4) Articles published worldwide on leptospirosis, focusing on unusual exposure conditions for leptospirosis, like cold, dry and altitude environments (e.g. Nepal and Russian arctic). The aim was to compare these results with probable cases acquired in Swiss mountain regions, and thus infer the likelihood of disease or pre-test probability among this specific population.

2.3. Data collection

2.3.1. Primary data collection

2.3.1.1. Questionnaire to the infectious disease specialists

Data for this study have been collected primarily through a questionnaire sent to infectious disease specialists in Switzerland in October 2014. Key questions aimed at determining leptospirosis cases diagnosed in Switzerland in the past years, and the location of infection.

Additional information about signs, symptoms, route of infection, severity of disease, age, sex, diagnostic methods and treatment was obtained subsequently through direct contact (telephone or email) with infectious disease specialists who reported positive cases, but was not requested in the original questionnaire.

The report of non-cases was also demanded in the questionnaire.

2.3.1.2. Other sources of information

Beyond case collection through the questionnaire, exchanges on the topic of leptospirosis with colleagues of different medical fields helped to further assess the presence of the disease in Switzerland, and aimed at accessing data on cases that were not reported in the questionnaire.

We also interviewed laboratory specialists in the field of leptospirosis in Switzerland by telephone or in direct contact.

Beyond borders, direct contact with specialists in the field of Leptospirosis was made, as for instance with the GLEAN chair and WHO representative, with specialists from France [34], from the Netherlands [35] and from the Center of Disease Control in Atlanta.

This was done throughout the complete study time, from August 2014 until August 2016, in an informal yet relevant and confidential way.

2.3.2. Secondary data collection

2.3.2.1. Federal Office of Public Health

Information on leptospirosis cases in Switzerland was reported by laboratories to the Federal Office of Public Health from 1989 to 1999. The register excerpt gives support to an incidence rate calculation for this period of time. After 1999, leptospirosis was not a notifiable disease anymore, thus no further data exist.

2.3.2.2. Federal Office of Statistics

The Federal Office of Statistics in Switzerland has collected the diagnosis of all hospitalized patients throughout the country since 1998.

In this study, we reviewed the register from 1998 until December 2014, the last available amount information. The diagnosis of leptospirosis among hospitalized patients are divided into three codes:

A270: "Leptospirosis icterohaemorrhagica "Weil-Disease"

A278: "Other forms of leptospirosis"

A279: "Leptospirosis nicht näher bezeichnet"

The first code, A270, concerns the most severe form of leptospirosis, called "Weil-Disease", the codes A278 and A279 specify milder forms, yet severe enough to need hospital treatment. A clear distinction between A278 and A279 has not been considered as pertinent, so these two categories were counted together.

The access to these data on internet is free (annual reports of the Federal Office of Statistics). Yet the limitations of available data render us unable to collect any information about the site of infection (autochthone vs imported), route of infection or name/place of the treating hospital. Further epidemiologically relevant data about the patient's living context, gender, exact age, occupation and the clinical course of the disease and its treatment were kept strictly confidential and unavailable for the current study.

Note that only hospitalized cases are registered by the Federal Office of Statistics, with in contrast the data collected by the Federal Office of Public Health, where the cases were reported by laboratories and doctors.

2.4. Clinical definitions

2.4.1. Range of data and classification

All cases of leptospirosis infection diagnosed in Switzerland within the past years were taken in the study and entered into our data base until December 2015. No limitation towards the past was set.

A subsequent classification was made among confirmed vs probable cases and locally acquired vs imported cases. If known, the exact location and route of infection were noted.

2.4.2. Case definition

2.4.2.1. Confirmed vs probable cases

Confirmed cases are patients with laboratory results that show either:

- a positive PCR (blood or urine)
- a seroconversion: fourfold or greater increase in *Leptospira* spp. titers in two serum specimens taken at least 10-14 days apart (acute and convalescent phase serums)
- a positive MAT Test (titer of 1:800)
- isolation of *Leptospira* spp. from a clinical specimen
- detection of *Leptospira* spp. in tissue by direct immunofluorescence

Suspected /probable cases are patients that present signs and symptoms compatible with Leptospirosis and either:

- a single positive serology
- agglutination titer of 200 but < 800 by MAT
- involvement in an exposure event (e.g. adventure race, triathlon, surfing etc.) with known associated cases

2.4.2.2. Local vs imported cases

A further classification between imported and locally acquired cases was crucial in establishing a map of locally infected cases in Switzerland.

Locally acquired cases were patients who acquired the disease in Switzerland. Imported cases were patients that imported the disease from neighbouring countries in Europe or from overseas, typically from tropical countries. Determining criterion was the time of incubation of the disease that can last up to 29 days after exposure. All collected cases were diagnosed in Switzerland.

Borderlines for exact localization of infection within Switzerland were rendered difficult in patients working for example in two different cantons.

Results based on the questionnaire, on the literature research and the direct information from colleagues enable us to make this distinction between locally acquired and imported cases. Based on this information a map of locally infected cases could be drawn and observational analysis could be described.

This was not possible with data from the secondary data collection, because information from the federal office of public health and from the federal office of statistics did not make the distinction between locally acquired cases or imported cases.

2.5. One Health approach

As leptospirosis is a zoonosis, a One Health approach for this study was essential.

Veterinary colleagues from the Vetsuisse Faculty at the University of Bern were contacted and asked about the current situation of the disease among domestic animals in Switzerland. Harboring the national reference laboratory for leptospirosis, the Institute of Veterinary Bacteriology (IVB) kindly offered us support for this study and offered free analysis of material for the presence of leptospirosis if needed.

A further contact has been made with veterinary colleagues from the Center for Fish and Wildlife Health in Bern (FIWI), who were assessing presence of disease among feral animals, which can act as “sentinel” in detection of emergence and reemergence of many diseases [36, 37]. Their project was supported by the Federal Food Safety and Veterinary Office. They kindly offered us support in analyzing any further material for the presence of leptospirosis if needed. A unique collaboration between medical and veterinary research in assessing presence of leptospirosis in Switzerland was born.

In order to assess the presence of the disease among rodents which can be healthy carriers of the disease and potential reservoirs, responsible of shedding live leptospores into environment leading to secondary “host” infections, we asked a rodent biology specialist about the presence of the disease in this category of animals.

Eventually, in a mountain valley where three cases of human leptospirosis were suspected in Mai 2013, the local wildlife guard was asked about current ongoing diseases

in local feral animals. He also collaborated in catching mice and was asked to report and send any suspect animal to FIWI for analysis.

3. RESULTS

3.1. Literature review

3.1.1. Human leptospirosis cases in Switzerland

Reviewing Swiss literature revealed 17 (53%) out of a total of 32 collected local cases, thus playing a major role in the assessment of the disease in this study.

Publications came from Geneva (3 articles, 3 different cases) [14, 23, 38], Lausanne (2 articles on local cases (1 case each) [39, 40], 1 article on imported cases (4 cases¹) [24]), Zürich (Bremgarten) (1 article, 3 cases) [21], Luzern (1 article, 1 case) [41], Basel (1 article, 2 cases)[15] and Ticino (1 article, 7 local cases, 1 imported) [42].

The first article found is “*Leptospirose ictéro-hémorragique*” in the *Revue Médicale Suisse Romande* in 1984 by Jacques MC, the latest reveal a cluster of leptospirosis in surfers on the Reuss in 2015.

Details about patient history, clinical course of the disease and relevant epidemiological information collected from the Swiss literature review were entered in our data base and are listed in the Annexes 2a and 2b. These articles helped to form a better understanding of the disease pattern and allow to compare the signs and symptoms of imported vs locally acquired cases. They will be further described and analysed in the following chapters.

3.1.2. Animal leptospirosis in Switzerland

Leptospirosis is a well-known disease among veterinarians and a subject of research at the Vetsuisse Faculty in Bern and at the Center for Fish and Wildlife Health in Bern.

Dogs: At the time of writing, the role of dogs in the epidemiology of leptospirosis in Switzerland is being assessed by the department of clinical veterinary medicine at the Vetsuisse Faculty University of Bern. Indeed, an unusually high incidence of canine leptospirosis has been observed in Switzerland between 2003 and 2012, with up to 28.1 diagnosed cases /100'000 dogs/year [43].

Beavers and feral animals: A further unusual finding was the presence of leptospirosis infection among beavers [44]. This led to further investigation by the Fish and Wildlife Institute in Bern who assessed the role of four feral animals (beaver, small rodents, foxes and wild boars) in the epidemiology of leptospirosis in Switzerland. These findings will be further explained in the corresponding chapter in the “Discussion”, based on the Institute’s report published in December 2015 [37].

Small mammals: An article reports the study of smalls rodents and shrews caught in the city of Zürich [45]. The prevalence of *leptospira* spp. was 12,6%, substantially lower than in Detroit and Baltimore. This moderate rate was comparable to the incidence rate in European rural regions.

¹ The article from Lausanne concerning 4 imported cases has not been entered in the list of locally acquired cases. Yet it is mentioned here as it will be an important point of comparison for the later discussion.

Horses: Seroprevalence of leptospirosis was tested among healthy horses between 2006 and 2008: 58,5% (n=360) had antibodies against leptospire [46].

Capricorn: The most surprising finding was the report of leptospirosis seroprevalence among capricorns in the Swiss Alps: 7,9% of tested capricorns between 2008 and 2010 carried antibodies against leptospire [47, 48].

3.1.3. Leptospirosis in Europe

Among articles assessing this disease in Europe we focused on countries bordering Switzerland: France, Germany, Italy, and Austria. No article was found about leptospirosis in Liechtenstein.

The annual epidemiological report from ECDC Stockholm (2014) was used as a further support, together with reports from the Netherlands, since this country not only harbors a national reference center for leptospirosis but is also one of five reference centers for the WHO.

3.1.3.1. ECDC Stockholm (2014)

At the time of writing at the end of 2016, the website of ECDC Stockholm [49] refers to the annual report of 2014 concerning the monitoring of leptospirosis.

This annual report 2014 of ECDC Stockholm concerns confirmed reported leptospirosis cases from EU/EAA from 2008-2012 and states that leptospirosis remains a rare disease in Europe [49]. The number of confirmed cases remains static in most EU countries, and infections are predominantly found in adults, affecting more men than women. Most cases were diagnosed in working age 24 to 64 years old, presuming that this reflects the predominance of cases in occupational risk groups such as farmers and people who do water-sports. The report also concerns travelers abroad. 10 deaths were reported and the seriousness of the disease might be under represented, since the completeness of mortality attribution is unclear. Infections are sporadic, strongly seasonal with higher rates in summer and autumn, and occur through occupational and recreational exposure. No outbreaks were reported.

3.1.3.2. France

The neighboring country France holds a national reference center for leptospirosis (Centre National de Référence de la Leptospirose), and their assessment of the disease contributes to the epidemiological surveillance of human leptospirosis, not only in metropolitan France but also in the overseas departments. In 2014, over 4000 specimens have been analyzed by serology or PCR. The CNR is also one of the 5 reference centers for WHO, and is involved in research for better diagnostic methods.

Their annual report 2015 (for the year 2014) reveals the incidence rate per department from 2008 until 2014. Incidence rates per 100'000 inhabitants for departments neighboring Switzerland are:

Alsace:	0,38/100'000 inhabitants in 2013; 0,54/100'000 in 2014
Franche-Comté:	3,73/100'000 in 2013; 1,78/100'000 in 2014
Rhône-Alpes:	1,43/100'000 in 2013 and 0,78/100'000 in 2014

This report also confirms the seasonal character of leptospirosis infections with peaks observed in August and September.

Among the MAT results, the serogroup Icterohaemorrhagiae was predominant, followed by Canicola, Grippotyphosa and Australis.

Overall incidence has doubled in France over the past years. In 2014, it was estimated at 0,98/100'000 inhabitants, the highest incidence rate since this surveillance exists in metropolitan France. In 2013 already an unusually high incidence has been observed. Climate warming and increase in "at- risk" activities such as water sports are called forth.

3.1.3.3. Italy

The epidemiologic trend of human leptospirosis was assessed in Italy between 1994 and 1996, based on 222 reports to the Italian Ministry of Health. Among all cases, 126 were confirmed by the National Center for Leptospirosis or one of the 12 Regional *Leptospira* Laboratories [50].

The majority of cases was observed in the northern regions of the country (83,8%), and mostly in males (88.9), findings that correspond to reports to the Italian National Center for Leptospirosis assessed from 1986 until 1993 [51]. A peak of incidence was observed in August, and the fatality rate was as high as 22.6%. Out of 103 patients for whom the place of residence was known, 98 (95.1%) lived in rural areas or devoted themselves to occupational or recreational activities at risk.

Antibodies against serovars icterohaemorrhagiae, poi, copenhageni and brattislava were the most frequent.

3.1.3.4. Germany

In Germany the documented history of leptospirosis began in 1886 with Adolf Weil whose name has been given to the severe form of leptospirosis [52]. From the 1920s to 1960s, several thousands of persons got infected in agriculture-associated epidemics. The disease is notifiable since 1962 (since 1958 in the DDR) [53].

An article published in 2005 then assessed the disease between 1962 and 2003, based on national surveillance data and by conducting a questionnaire-based survey from 1997-2000 [53]. The mean annual incidence decreased steadily from 0.11/100'000 population (1962-1967) to 0.04/100'000 ($p < 0.001$) population in 1997. Then, the incidence increased again from 1998-2003, with an incidence of 0.06/100'000 population ($p = 0.01$). Of the 126 reported patients from 1997 to 2000, 10 patients died (90% men, case fatality 8%). The causes of these deaths were: multiple organ failure (including fever, renal failure and jaundice) (6 cases), massive pulmonary hemorrhage (1 case), intracerebral hemorrhage (1 case), cardiopulmonary failure (1 case), and acute respiratory distress syndrome (1 case).

An average of 87 clinical leptospirosis cases was reported each year in Germany (range 46-177) to the Robert-Koch Institute [54]. These results lead to the assumption that leptospirosis is rare in this country, yet the underlying incidence of clinical or asymptomatic infections is unknown.

A recent article was published on leptospirosis in South-Germany, in Baden-Württemberg, a state bordering Switzerland. The study revealed risk factors for local human *Leptospira* seropositivity by using a population based cross-sectional zoonosis survey during 2008-2009 [55]. 42 (4.2%) out of 1007 participants were seropositive, 19/446 were men, and 23/561 were women. Contact with pet rats showed a relative risk of 13.9 (CI 4.8; 25.3 adjusted for specificity and sensitivity of the ELISA test), with guinea

pigs a RR of 3.0 (1.1;7.4), with cattle RR was 3.7 (1.3;9.6), with poultry RR was 3.6 (1.3;8.6), with livestock RR was 2.3 (1.1;4.9) and for forestry worker RR was 9.2 (2.6;21.4).

It is of interest regarding our study that none of the participants had ever been diagnosed with leptospirosis, yet 45 had experienced symptoms such as scleral icterus (12), dark urine (25), liver inflammation (8) or kidney failure (7), symptoms which could have been caused by *Leptospira* infection. Seropositive patients with severe symptoms may frequently not be diagnosed as leptospirosis cases, since three times as many participants with prior symptoms were seropositive (RR=3.4 (1.3; 8.3)).

This study invites physicians to consider leptospirosis as a differential diagnosis since most symptomatic leptospirosis patients may neither be diagnosed nor reported.

3.1.3.5. Austria

The prevalence of antibodies against *Leptospira* spp. was assessed in a cross-sectional survey in Austria, from April to June 2009. 400 healthy individuals were tested, predominantly males aged 18-57 years. A positive serological screening results was observed for 88 (23%), with most frequently serovars Canicola (16,5%) and Hardjo (11.8%). This seropositivity rate was unexpectedly high and comparable to findings in tropical and subtropical countries of high endemicity [2]. Until then, human leptospirosis was considered a rare disease in Austria, with 9 cases reported in 2011, thus an annual incidence of 0,13/100'000 population. The national rate for leptospirosis ranged from 0 to 3 cases in the 1990s, from 8-11 in the 2000s.

In the year 2000, 149 hunters with a mean age of 50 years were tested in south-east Austria. A seropositivity rate of 10% (MAT>100) was found in these hunters compared to a control group of 50 individuals with a seropositivity of 0%.

Comparing the findings of these two studies may indicate an increase of seropositivity to *Leptospira* spp. in Austria from the year 2000 to 2009. The article also stipulates that surveillance of clinical cases and hospitalizations may greatly underestimate the true rates of infection.

3.1.3.6. The Netherlands

The Netherlands harbor a national surveillance system and a reference laboratory. leptospirosis in humans has been a mandatory notifiable disease since 1928. A 4-6-fold increase in autochthonous cases in 2014 alarmed the public health authorities.

A surveillance and outbreak report [13] describes the marked increase in leptospirosis infections in humans and dogs in the Netherlands in 2014. It is interesting to see the coincidence of increase of the disease in both dogs and humans. This report also states that most autochthonous cases were linked to recreational exposure such as fishing and swimming, followed by occupational exposure.

A possible attribution of increased incidence rate was given to a mild winter in 2013-2014 followed by the warmest year in three centuries, allowing rodents and *Leptospira* spp. to survive better.

A current study conducted by the KIT (royal tropical institute) in Amsterdam will further assess the evolution of the disease in Europe. The results have not been published yet.

3.1.4. Leptospirosis worldwide: focus on altitude and cold regions

In order to be able to compare the exposure of our Swiss cases with similar weather and altitude conditions in other parts of the world, the literature was searched beyond borders.

3.1.4.1. Altitude/Mountains

In the US, a study in employees from the Great Smoky Mountains and Rocky Mountain National Parks in the years 2008-2009 showed an incidence of infection with leptospirosis of 5.7% [56].

A study on Samoa islands revealed that altitude is not a limitation factor for the disease [57].

In Katmandu, Nepal, situated at 1300m above sea level, a further study investigated 876 patients in cold, dry winters (December to February) and in hot monsoon seasons (June to September) [58]. They assessed patients coming to the emergency ward with fever. 36 patients were diagnosed with leptospirosis, half of which originally thought to be enteric fever. Cases were detected in both seasons, cold, and monsoon season. Yet, we must consider that IgM antibodies may persist for a year or longer, and present a serological scar, which may interfere with specificity.

In the north-east Italian Alps, close to the border to Switzerland, an Italian study showed a seroprevalence of 10-12% among farmers and foresters in the north-east Italian Alps [2]. This suggests presence of disease in altitude, not only in tropical countries, but also in Europe.

3.1.4.2. Cold

In the extreme north, a Russian study conducted above the polar circle showed a prevalence of *Leptospira* antibodies of 9-30% among the population in the selected district of Yakutia [59]. Human leptospirosis was observed in other regions as well. Natural reservoirs were identified among several mammal species, and persons at the highest risk of infection were deer breeders and hunters. This study revealed that *Leptospira* bacteria can survive under low temperatures, and it also showed the existence of very stable foci of this disease in circumpolar regions.

A recent study analyzed survival and virulence of pathogenic *Leptospira* spp. strain Icterohaemorrhagiae artificially set in different environments [60]. The samples were for instance stored for 20 months at 4, 20 and 30° C. Interestingly, the strains survived for a mean time of 130 days at 4°C, and kept its virulence despite other unfavorable storage condition such as pH<6.

3.2. Results of the questionnaire and from other sources of information

3.2.1. Questionnaire

Among 178 questionnaires sent out to infectious disease specialists in Switzerland in October 2014, 28 (16%) responded, either with cases or «non-cases».

Among the 28 case-responses, 6 came from University hospitals (23%). Adult infectious disease department responses came from Geneva (HUG), Lausanne (CHUV), Zürich (UZH) and Basel (USB), thus from 4 of 5 university hospitals in Switzerland. Informal information was received from the fifth university hospital, Bern, but not

through a direct response to the questionnaire. Paediatric infectious disease specialists from the university hospital of Geneva (HUG) and Bern (Inselspital) responded as well.

Further 6 responses (21%) came from state hospitals of the canton of Fribourg, Schwyz, Zug, Luzern, Olten and Nidwalden. Other hospitals: Nyon (GHOL) in Vaud, Triemli and Waid in Zürich, Spital Thun in the canton of Bern, and Biel and La Chaux-de-Fond in the canton of Neuchâtel accounted for 6 more responses (21%).

Eventually, 4 independent infectious disease specialists responded from the canton of Ticino (2), Luzern (1), Zürich (1), and the medico cantonale from Ticino, accounting for 18 % of responses.

A few laboratories, contacted through the mailing list for the questionnaire responded to us as well. We received 5 responses this way (18%), from the laboratory Synlabs and Unilabs in Ticino (3 responses) and Labor BABS in canton Bern responded this way too.

3.2.2. Other sources of information

Direct contact with infectious disease, internal medicine and intensive care specialists, added information on 4 imported cases (2 confirmed and 2 probable) in Lausanne (CHUV), one locally acquired and one imported case from Triemli hospital in Zürich, 3 locally acquired cases in Geneva (HUG), and 3 locally acquired probable cases at the Center da Sanda Val Müstair in Graubünden. Additional “no-cases” were added to this list as well, as summarized in the corresponding table (Table 1).

Laboratory information was gathered at Labor Team W in St. Gallen. They perform about 30 Elisa serological tests for Leptospirosis per year. This number did not increase in the last years, and positive results are extremely seldom.

The “Zentrum für Labormedizin” in St. Gallen used to perform the MAT tests in the past, but now, blood samples are sent abroad, since the livestock of *Leptospira* spp. species necessary for this exam was too complicated to maintain.

3.2.3. Cases and non-cases

Our results were then further subdivided into “cases” and “no-cases”. Among 28 responses from the questionnaire, 10 reported between 1-5 cases with a total of 21 cases, and 18 responses responded for “no-cases”. Some responses were overlapping, for example different infectious disease specialists answered for the same region or hospital. Among paediatric infectious disease specialist’s answers from the university hospitals in Geneva and Bern were gathered, both reporting no cases. 2 “non-cases” were added through direct communication with infectious disease specialists and medical practitioners.

Case	Canton	Location	Result
1	TI	Lugano	no cases since 2011
2	TI	Savosa	no cases
3	SZ	Schwyz	no cases
4	TG	Thurgau	no cases
5	NW	Nidwalden	no cases
6	ZG	Zug	no cases
7	LU	Luzern	no cases
8	AG	Olten	no cases
9	BE	Bern	<i>no paediatric cases</i>
10	BE	Bern	no cases
11	BE	Biel	no cases * 1)
12	BE	Biel	no cases
13	BE	Thun	no cases since 2012
14	BE	Spiez	no cases * 2)
15	FR	Fribourg	no cases
16	NE	La Chaux-de-Fond	no cases
17	GR	Chur	no cases
18	GR	Scuol	no cases
19	ZH	Erlenbach	no cases
20	GE	Geneva	<i>no paediatric cases</i>

Table 1 “no cases”, collected through the questionnaire in October 2014 and through other sources of information. No time limit was set.

3.2.4. Autochthonous vs imported cases

Among the 21 cases reported to us through the questionnaire, 14 were autochthonous cases and 9 patients imported the disease from other European or tropical countries. The table below shows the location of infection, route of infection, gender, age and place of diagnosis and treatment (canton) of the imported cases. An additional case (n°10) was gathered by Swiss literature review.

Case	canton	location of infection	infection route	date	gender	age
1	GE	France (Drome)	watersports (canoeing)	8.2014	F	41
2	GE	Malaysia	swimming in river	8.2014	M	16
3	VD	Thailand	watersports (fell in water)	8.2014	F	43
4	VD	Thailand	watersports (fell in water)	8.2014	M	15
5	VD	Thailand	watersports (fell in water)	8.2014	M	28
6	VD	Thailand	watersports (fell in water)	8.2014	F	17
7	BS	Ecuador	<i>unknown</i>	2009		
8	ZH	Czech Republic	watersports	2013	M	young
9	ZH	Thailand	<i>unknown</i>	2012	M	46
10	TI	Serbia	bathing in river	<2000	M	35

Table 2 Imported leptospirosis cases diagnosed and treated in Switzerland

For the 14 autochthonous cases, gathered through the questionnaire, a variety of responses were given. Some infectious disease specialists mentioned infections having recently occurred, other mentioned cases without precise dates or details.

In addition to the cases collected through the questionnaire 17 cases were gathered by direct contact with physicians or in the literature. All collected cases and details are listed two tables: one focused on the diagnosis of leptospirosis, one focused on the clinical course of the disease. Because of their large size they are attached in the appendices (app. 2a and 2b). Their content will be further described in the following chapter.

3.3. Descriptive epidemiology of locally acquired leptospirosis in infected patients (autochthonous cases) from 1970 until 2015

3.3.1. General information

Age

Patient's ages ranged from 25 to 88. The mean age is 50,8. Ten patients were <40 years old (41% out of 24 patients from whom we know the age), three patients over 70 years old (13% out of 24), and 11 between 50 and 70 (46% out of 24).

Infections in children were not described in the locally acquired cases, nor reported by paediatric infectious disease specialists in Geneva and Bern, but similar signs and symptoms have been pointed out in a 15-year-old teenager returning from Thailand.

Gender

Among the 31 patients 20 were men (65%), 6 women (19%), and 5 of unknown gender (16%).

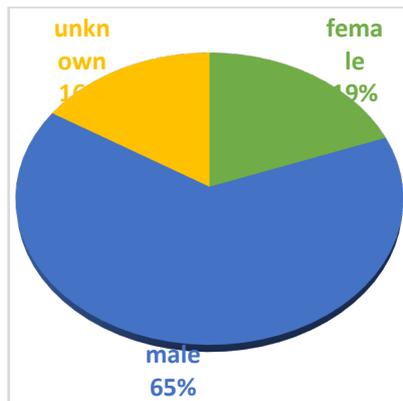


Figure 2 Gender (n=31)

Treatment setting

Out of 31 patients listed in our findings, 3 patients were certainly treated ambulatorily. It is not clear whether all other 28 patients required hospitalization, but it can be supposed based on symptoms, signs, laboratory results and complications described in the reported cases.

Diagnosis

Out of 31 cases, 21 are confirmed cases (serology or PCR). Three cases are probable cases (single serology), further 7 lack information on status or diagnostic method. Serology was performed in most cases: 20 out of known 24 cases, 4 diagnoses were made with PCR in blood and /or urine. In one case, serology was twice negative with a positive PCR in blood.

Serovar

12 MAT were performed, showing *L. icterohaemorrhagiae* in 4 cases, *L. grippityphosa* in 4 cases, *L. australis* in one case, combined *L. grippityphosa* + hadjő in one case, and *L. australis* + bratislava in another. *L. canicola* was diagnosed in one case.

3.3.2. Clinical signs and symptoms

Among 22 patients from whom we have collected information on initial signs and symptoms, fever was mentioned in 18 patients (80%). Other “flu-like Symptoms” like myalgia, arthralgia and/ or malaise were reported in 18 of 22 patients (80%), additional headache was noted in another 10 patients (45%). Four patients described the headache as “severe headaches”, sometimes accompanied by photo-phonophobia, and with meningeal sign in two patients. Abdominal/epigastric pain and gastrointestinal symptoms like nausea, vomiting and/or diarrhoea were reported in 6 patients (27%). Cough was noted in one person, dyspnoea in another. Icterus was described in 5

patients (23%). Conjunctivitis was noted in 2 patients (9%). Petechiae were described in 2 patients (9%).

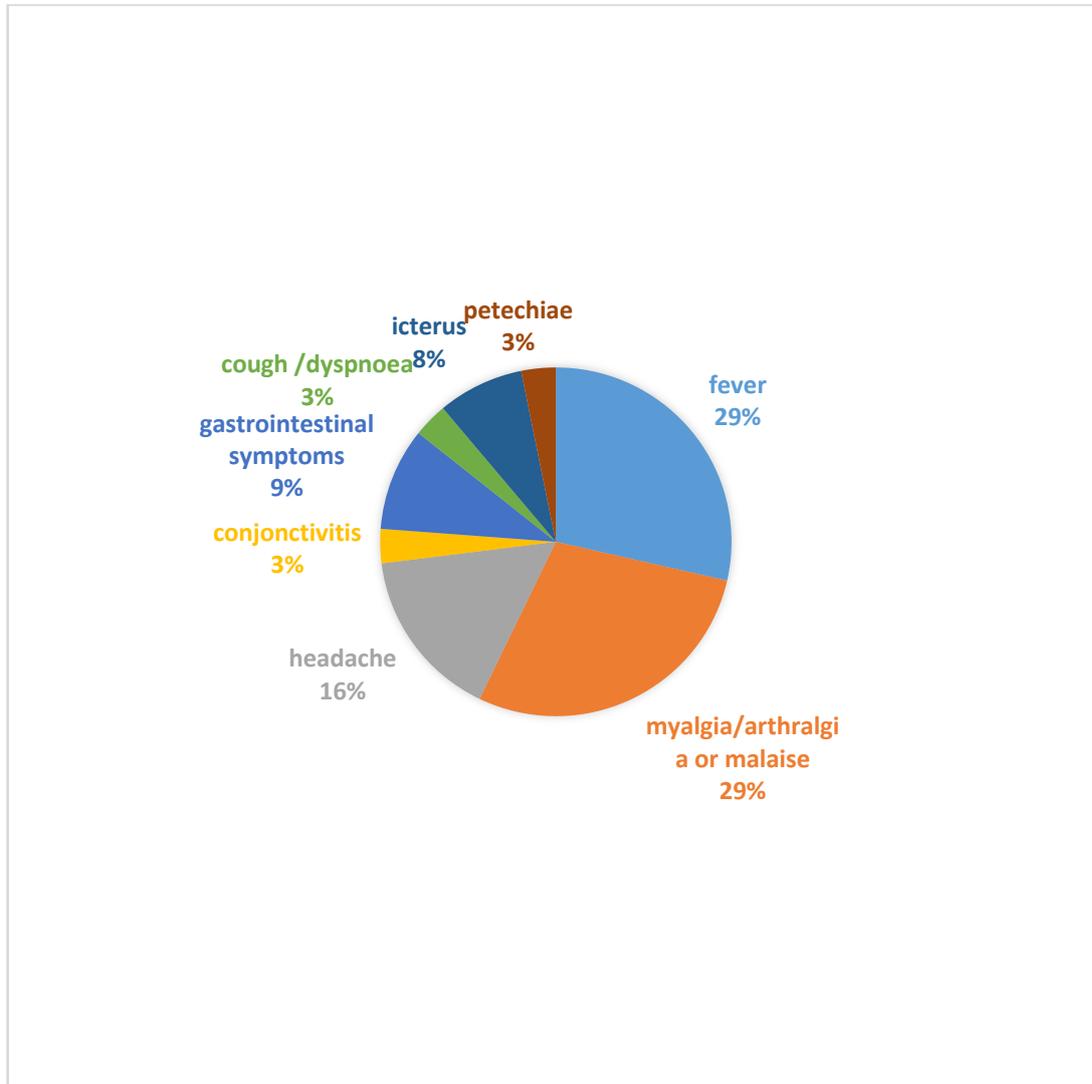


Figure 3 Signs and symptoms of patients who acquired leptospirosis in Switzerland between 1970 and 2014 (n=22)

3.3.3. Clinical laboratory results

Among 24 patients from whom we know laboratory results, 11 patients (46%) showed abnormal liver enzyme results, ranging from slight elevation (4 patients) to acute hepatitis/liver failure (at least 2 patients with multi-organ failure). An association with elevated bilirubin /intrahepatic cholestasis was noted in 3 patients (13%).

Renal injury was noted in 16 patients (67%), ranging from slight elevation of creatinine (1 patient) to acute renal failure in 15 patients (63%), many of which required dialysis (in 5 patients dialysis was explicitly reported, ICU treatment was described in another 4 patients which probably underwent dialysis in the context of acute renal failure. Thus, dialysis can be supposed in 9 patients out of 15 with acute renal failure (38% of 24 patient data). One patient, with diabetes type II as comorbidity, needed dialysis over many months after initial diagnosis.

Thrombocytopenia or pancytopenia is a classical finding, as noted in 10 out of 24 patients (42%) from whom we have information on complication of disease.

CRP ranged from <5 to 313 mg/L, and WCB was either normal, leukopenia or leukocytosis with left shift.

3.3.4. Severe acute complications

Acute headaches with meningeal signs were the main reason for hospitalization for two patients, one female and one male. Another female patient complained of acute headaches and loss of concentration, and underwent a cerebral MRI without clear diagnosis.

As previously said, acute renal failure was observed in 15 patients with subsequent need for dialysis for many of these patients requiring ICU treatment. One patient, with diabetes type II as comorbidity, needed dialysis over months after initial diagnosis.

The severity of liver injury was not assessed, but frequent elevation of liver enzymes was noted, ranging from slightly elevated to 4x the normal values. In two cases multi-organ failure was clearly described, this might however concern more patients (considering signs/symptoms and laboratory results).

Jarish-Herxheimer reaction on antibiotic therapy was described in 4 out of 24 patients (17%), leading to intermediate or intensive care support.

The term “septic shock” or “sepsis” was mentioned in 4 cases, although the diagnosis might concern further patients with renal and hepatic impairment associated with coagulopathy and fever and treated in ICU settings.

Severe haemorrhage due to coagulation disorder is not seldom, and one female was admitted to the ICU and intubated with massive pulmonary haemorrhage, for which no bleeding source was found in bronchoscopy. One patient died of cerebral haemorrhage in the 1970ies.

One patient suffered from multi-organ failure with very little survival chance (mortality was calculated to 90% (APACH II SAPAS II scores)) and treated in the ICU with plasma exchange and high-volume hemofiltration, with a total of 45 days of acute intensive care unit stay plus another 25 days of hospitalization. Haemorrhagic bronchial secretions caused several respiratory arrests, and he also underwent abdominal surgery after developing severe CMV colitis. He also needing transient pacing for extreme bradycardia. He eventually recovered.

Arrhythmias and myocarditis with elevation of Troponin was noted in 3 patients (13%).

One patient with a milder clinical course of disease developed a chronic post-infectious polymyalgia after suspected Leptospirosis infection and treatment. To date (2016), he is still dependent on corticosteroid treatment and developed heart failure of unclear origin.

As mentioned, one patient died of cerebral haemorrhage, and another death of a patient with coagulopathy and myocarditis was reported in 1984, thus death accounting for 2 out of 31 outcomes (6%).

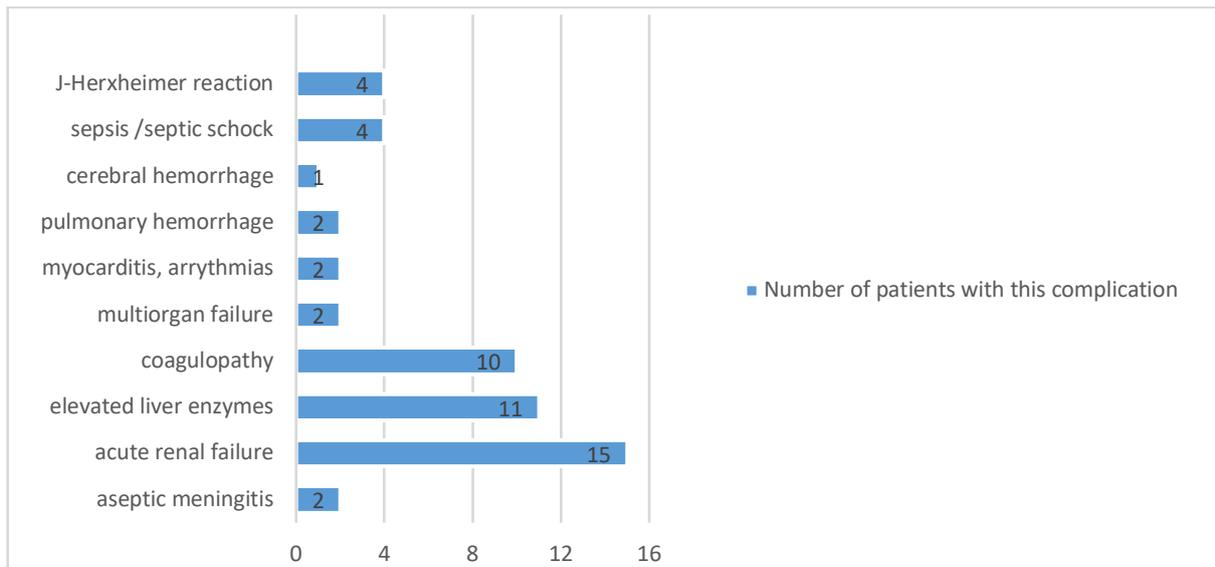


Figure 4 Disease complications of patients who acquired leptospirosis in Switzerland between 1970 and 2015 (n=24)

3.4. Localization, clusters and exposure assessment

3.4.1. Localisation

Among 31 locally infected patients, 5 acquired the disease in Geneva (16%), 7 in Vaud (22%), 3 in the canton of Basel (10%), 3 in the canton of Aargau (10%) (cases diagnosed in Zürich), 1 in the canton of Zürich (3%), 1 in Luzern (3%), 3 in the canton of Graubünden (10%), 2 in between Graubünden and/or Ticino (6%) (diagnosed in Ticino), and 6 in Ticino (20%).

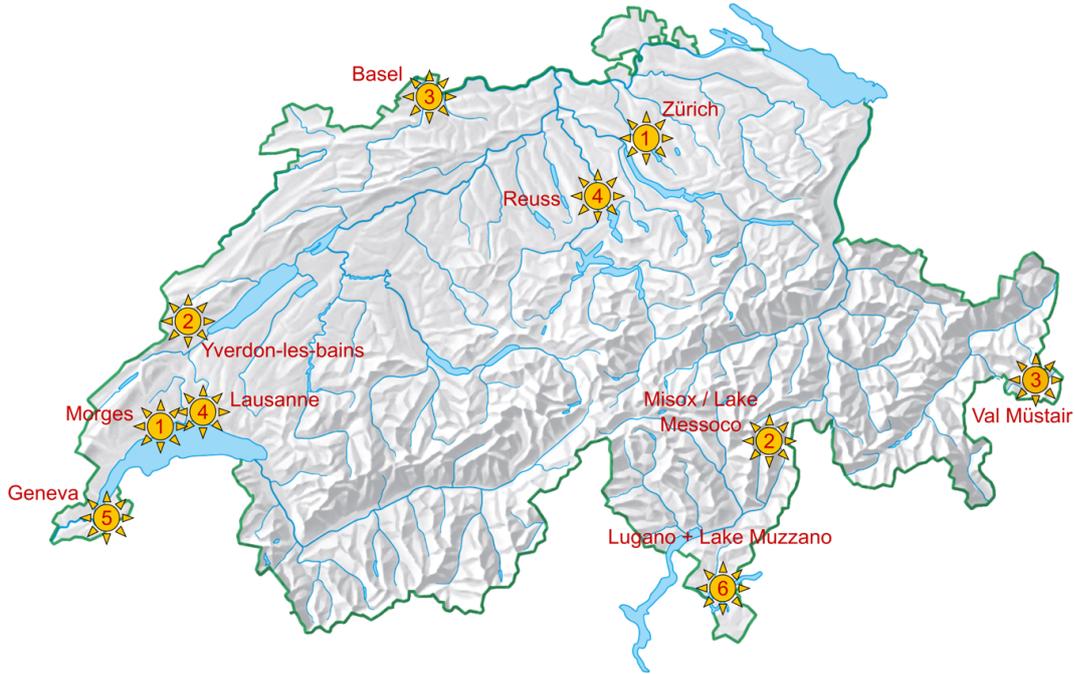


Figure 5 Map of locally acquired cases of leptospirosis in Switzerland, collected until August 2016 (not exhaustive). N=31, Cases = confirmed by PCR or serological titers, or probable cases)

3.4.2. Clusters

Four clusters could be identified. The first one in Geneva among fishermen, were 3 out of 15 local professional fishermen contracted the disease between September 2008 and June 2013, rendering the prevalence of Leptospirosis in this group of workers as high as 20%.

A further cluster was detected in the region of Bremgarten (Aargau), were 3 young surfers (two males and one female) aged from 32 to 34 acquired the disease in summer 2014 while surfing on the river Reuss. The cases were diagnosed in the Triemli Spital in Zürich.

A third cluster was suspected in a mountain valley, the Val Müstair, in the canton Graubünden. Three patients (two females and one male) of different ages and occupations, not related to each other, were supposedly infected by *Leptospira* spp. in the month of Mai 2013. A single serology came out positive in each case, and they were treated with doxycycline, but confirmation through repeated serology was then not pursued. Their clinical course of disease supported by the single positive serology classifies these cases as probable ones. These cases will be further discussed later.

Eventually, a fourth cluster of cases was reported in the canton of Ticino, in the early 1970s. Four patients contracted leptospirosis after swimming in Lake Muzzano. One of them died of cerebral haemorrhage.

3.4.3. Exposure

Among the clusters, 3 concerned water related activities. The first were fishermen, the second surfers and the third swimmer. Note that the first group concerns a professional activity, the two latter recreational activities.

The fourth cluster concerns patients living in the same rural environment in altitude. They are not related to each other, have different occupations, and live in three different villages of the Val Müstair. The first one is a hotelier, the second a teacher and the third one retired. A source of infection was not found for these patients.

3.4.3.1. Water related activities

In addition to the 3 fishermen, 3 surfers and 4 swimmers already described, 6 other patients have a “water-related” course of infection, rendering this route the principal risk factor noticed among our 31 patients (16 in 27 known infection routes, thus 60%). A patient died of leptospirosis after swimming in a river in Geneva in the year 1984, and another contracted the disease after cleaning an infected plastic swimming pool in the canton of Vaud. An additional surfer on the river Reuss, this time in Luzern in 2013, suffered of severe headaches before a diagnosis was made. Two patients had contact with rodents or rodent excrements on their boats, in Vaud and Ticino. A patient worked in a fishery and a farm, where the omnipresence of water and rodents rendered the route of infection somewhat unclear.

3.4.3.2. Contact with rodents or rodent excrements

In the 3 last mentioned patients, the route of infection is somewhat in between contact with infected water vs rodent excrements, their activity being boating and working in a fishery. Yet they reported contact to rodent excrements in these “at-risk” activities.

Another patient was infected by rat excrements found in his cellar, another through contact with a dead rat, one more was a gardener also in charge of cleansing parks.

Contact with a living rodent was noted in 6 patients. Two have rodents as a pet (one a rat, the other one a mouse), one patient got bitten by a wild dormouse that he tried to save from the road in the countryside where he lives, and another patient got bitten by a rat. Two patients are rabbit breeders.

3.4.3.3. Contact with other animals

One patient is a horse owner; whether this is the route of infection of the patient is however not certain. One patient had contact to dog urine as a suspected route of infection in Basel.

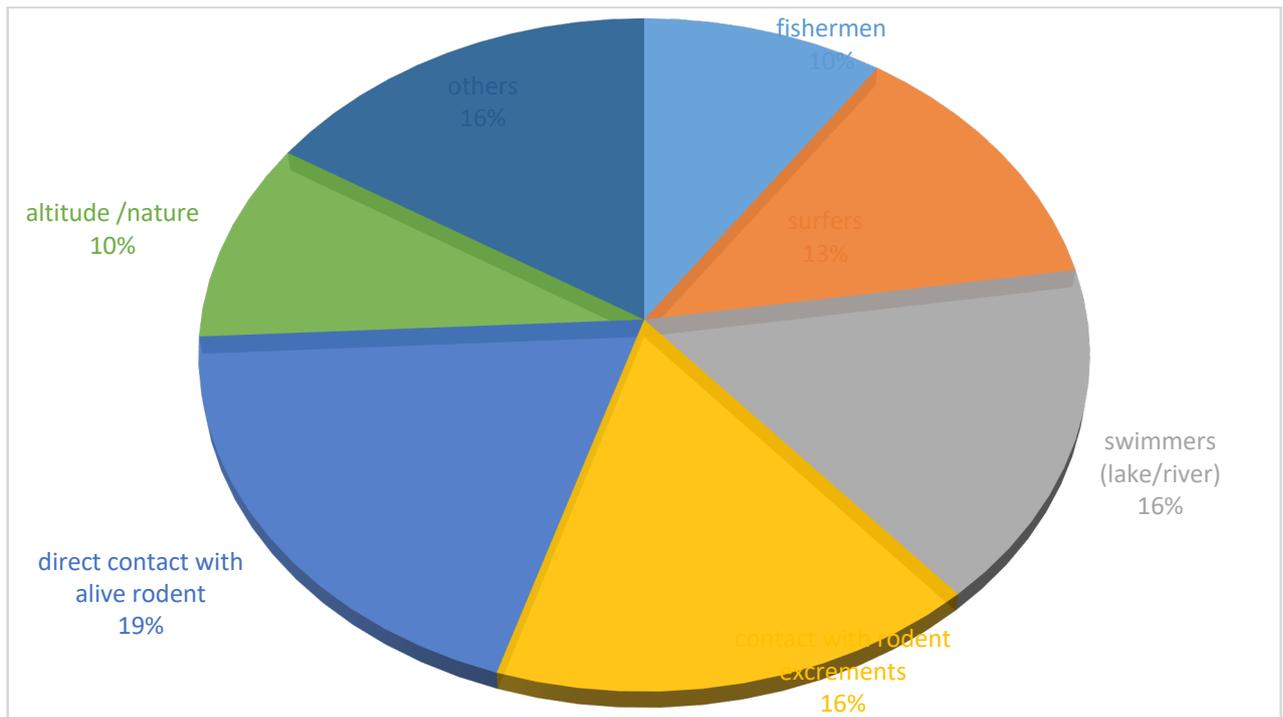


Figure 6 Infection routes of leptospirosis cases in Switzerland (1970-2015) (n=31)

3.5. Federal Office of Public Health and Federal Office of Statistics

3.5.1. Swiss Federal Office of Public Health

The Federal Office of Public Health reported an incidence rate of 0,08/100'000 inhabitants in the years 1989-1999 and was based on laboratory and doctors' reports. It includes ambulatory as well as hospitalized cases. After 1999, leptospirosis is not a notifiable disease any more.

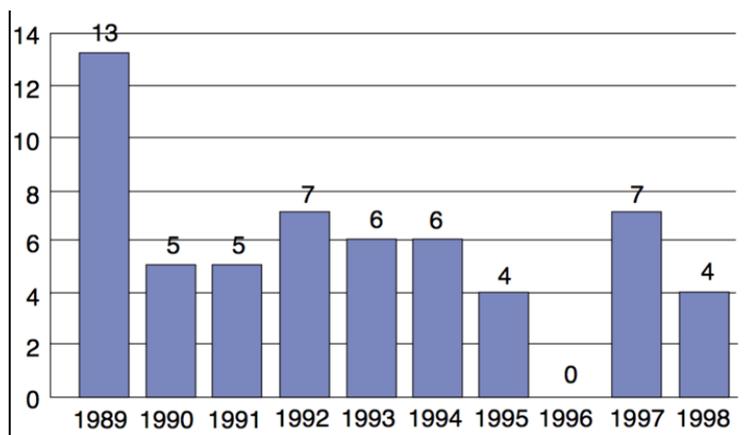


Figure 7 Reports of leptospirosis infections from Swiss laboratories to the Federal Office of Public Health from 1989 to 1998 [15]

(Source of this figure: [15] 2. BAG Registerauszug Labormeldungen zu Leptospireninfektionen 1989-1998. Bern: Abt. Infektionskrankheiten BAG, 1999)

In our study, contact was taken directly with public health authorities to assess the reasons for stopping a compulsory notification of leptospirosis after 1998, and to ask for any additional information.

The reason mentioned for stopping mandatory notification was the little number of cases per year.

From 1998 until December 2016, date of the final exchange on this subject at the time of writing, leptospirosis is not surveyed any more by these authorities. Yet, knowledge about ongoing studies by the Federal Food Safety and Veterinary Office exists. A couple of years ago, the foundation of allowing the French vaccine Spirolept, covering the serovar icteroheamorrhagiae, had been discussed.

Its introduction was refused, due to a lack of knowledge concerning the exact distribution of different serovars across the country. Thus introducing a vaccine covering only the single strain icteroheamorrhagiae was not considered relevant.

Even though the topic of leptospirosis in Switzerland is not assessed any more by the federal office of public health at the time of writing, it is not ruled out that the current study could be a basis for further discussion.

3.5.2. Swiss Federal Office of Statistics

Data from the federal office of statistics report 71 hospitalized cases of leptospirosis in Switzerland between 1999 and 2013. Thus, the mean annual rate is 4,73 cases/year.

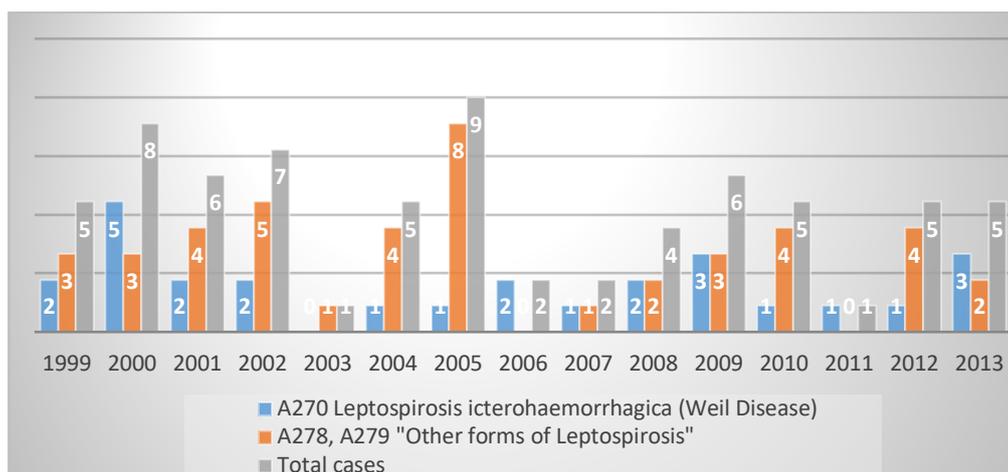


Figure 8 Number of hospitalized cases of human leptospirosis in Switzerland since 1999

The cases are subdivided into the leptospirosis icterohaemorrhagicae form (Weil disease) or “other forms of leptospirosis”.

No information is given on signs and symptoms, nor on the route of infection, localization of infection or name of the hospital who treated the case. We do therefore not know how many of these patients have imported the disease, or acquired leptospirosis in Switzerland. Information on diagnostic methods is lacking as well, rendering it impossible to classify into “probable” or “confirmed” cases.

Nevertheless, it is a reliable source of information, and the estimated incidence rate of hospitalized cases can be calculated at 0,06/100'000 population/year, using the mean Swiss population rate in this time frame: 7'516'296 inhabitants.

3.6. Veterinary medicine and biology

The Institute of Veterinary Bacteriology in Bern plays a major role in controlling and monitoring domestic animal leptospirosis in Switzerland, and houses the official federal laboratory for leptospirosis. It is thus a reliable source of information.

To date, the number of leptospirosis cases among cattle, horses and sheep are stable in Switzerland. Due to costs of the laboratory exams, farmers tend to send blood samples only if payed for by a veterinary health office (cantonal or federal), and single cases of leptospirosis might not be investigated /diagnosed by independent farmers. Yet no epidemic is known in any Swiss canton or region.

Feral animals are controlled by the Federal Veterinary Office, through the Centre for Fish and Wildlife Health at the University of Bern.

A recent study examined feral animals (beaver, foxes, wild boar and rodents) between 1998-2012 in a retrospective study, and between 2013 and 2014 in a prospective study, and reported a presence of the disease in all cantons and regions of Switzerland, including mountain areas. They did not however notice any increase in incidence of the disease in these populations [37].

Eventually, a study performed by the Small Animal Clinic in Bern showed that the number of hospitalized dogs at the veterinary hospital in Bern has increased significantly since 2010 [43]. Further investigation on leptospirosis is currently in process, from epidemiology in Swiss dogs to microbiologic research on endothelial cell responses to pathogenic *Leptospira spp* or inflammation and coagulation in canine leptospirosis [61].

3.7. One Health approach: example of the Val Müstair

In the present section we are describing 3 probable cases of human leptospirosis infected patients in a remote valley of the south-east Swiss Alps in 2013, and the following One Health approach to localize the disease and potential local public health issue.

3.7.1. Case presentation

In Mai 2013, three cases of human leptospirosis were suspected in the Val Müstair and treated at the Center da Sanda Val Müstair. These findings were curious, since first, this has never happened before, and second, the valley is located at an altitude between 1200 and 2000m, and none of these patients have travelled in any tropical country at that time. They did not have any contact to each other and lived in different villages, which also appeared rare for what could at first sight seem to be a local outbreak.

The three cases are classified as “suspected cases”, since they all have a matching clinic for leptospirosis and one single positive serology. This test was not repeated in an interval of 2 weeks to confirm a rise in titers, since the patients were treated with an antibiotic therapy, and initially recovered quickly. One in three patients presented long-term complications as we will discuss later.

Case n°1

The first case was a 60-year-old hotelier, who developed flu-like symptoms, followed 10 days later by a severe malaise, abdominal pain, vomiting, cough and night sweats after a brief period of recovery.

On physical examination general weakness and fever were observed, but no specific sign, in particular no rash or conjunctivitis, pulmonary or abdominal findings. Further vital signs such as heart rate, blood pressure and oxygen saturations were in normal range. Laboratory results showed a CRP raised to 212, while the white blood cells count was 7.7 (10e9/l) with 72% neutrophils. There was no liver or renal impairment. An initial chest X-ray did not show any infiltrate.

Because of fever, high CRP level and ill-looking patient, a battery of further diagnostic tests was made, none of which brought a clear diagnosis. In the meantime, the patient was put on broad antibiotic therapy. Fever ceased, but cough and general weakness persisted over time. The CRP slowly decreased from initial 212 to 140, 8 days later.

Night sweats and malaise persisted for over a month. An elevation of sedimentation rate had already triggered further examinations. Eventually, a positive leptospirosis ELISA serological testing brought a diagnosis of this illness. Even though a broad antibiotic therapy had already been given, treatment with doxycycline was started, leading to quick clinical improvement, including disappearance of important night sweats from which he had suffered for weeks.

At the time of reception of the positive *Leptospira* spp. serology result, 6 weeks of illness had passed and 4 weeks since initial medical consultation. During that time differential diagnosis such as malignancy, endocarditis, pulmonary or abdominal pathology, immunologic deficiency or disease were suspected and excluded by CT of chest and abdomen, bone marrow aspiration and immunologic examinations.

Note that the treating physician himself is a tropical medicine specialist and had worked in the tropics, thus knowing the clinical course of leptospirosis, with the bi-phasic evolution and unspecific symptomatology. Yet he was still surprised of the eventual finding.

Although acute illness resolved, CRP stayed high for a month and decreased to 18 only 5 months later. Fatigue also persisted, and the patient developed a post-infectious polymyalgia, and necessitated high-dose cortisone therapy for many months. He also developed heart failure of unknown origin and arrhythmias (complex ventricular and supraventricular extra systoles).

No specific contact to animals or rodents neither any at-risk activity such as hunting, fishing or water sports was reported. He lives in a rural environment and likes hiking.

Case n°2

Our second case is a 27-year-old, usually healthy, young female student.

She initially complained of weakness and earache, followed by strong headaches. Otitis media was suspected and she was treated with amoxicillin. While the headaches persisted, became severe and accompanied by loss of concentration, an MRI of the brain was performed to exclude any neurological abnormalities or infection.

On physical examination, no meningism was noted, nor any other specific signs other than subfebrile temperature. Laboratory results showed a very slightly elevation in liver enzymes, kidney function remained normal. Infectious parameters stayed relatively low, with a CRP < 5 and white cell blood count of 10.2 (10e9/L).

As weakness, subfebrile state, headaches and lack of concentration persisted and could not simply be attributed to tension headaches in a setting of university exams, further diagnostic tests were made including Leptospirosis serology.

The positive result of this serology in Mai 2013, shortly after a similar result in patient n°1, was found a month after the beginning of symptoms in this patient.

The young woman was then treated with doxycycline, and acute headaches quickly disappeared. She eventually fully recovered, yet after many months of latent weakness and diminished concentration.

A direct route of infection could not be found in this patient either. She reported a possible contact with what could have been mice or bat excrements when she was looking for clothes for a theater play in the attic of her school. After this event, the complete attic was cleaned, to ensure no further possible infection could occur this way.

Case n°3

Case n°3 is an 88-year-old very active healthy woman, who experienced a “flu like she never had before” in Mai 2013. Other relevant symptoms were cough and night chills. In the setting of previous positive leptospirosis results in case 1 and 2, a serology was immediately performed, with a positive result. Doxycycline was given and she recovered completely and quickly.

The clinical course of her disease is interesting. Two weeks prior to developing this extreme weakness and night sweats leading to Leptospirosis testing, a viral bronchitis had been suspected with mild symptoms, a CRP of 40 and a normal blood count. She completely recovered and was symptom-free for a week before the second stronger illness phase appeared. Note that at that time, laboratory results were a CRP <5, normal white cell blood count, and slightly elevated liver enzymes.

She eventually fully recovered, possibly owing to a quick diagnosis and treatment.

She is a cat owner and active gardener at home, and did not travel or experience a specific at-risk, water related activity or rodent contact other than mice brought home by her cat. She reports presence of a lot of birds (swallows) who tend to produce quite a lot of dirt around her house, which is not unusual. She is otherwise an active sport performer in the natural outdoor environment in which she lives.

Exposition - Val Müstair

The exposition of these three patients is nature, with proximity of the Swiss national park and close cohabitation with feral animals through the geographical mountain setting. None of them were farmers though, and all lived in different villages with no direct contact to each other.

None of the patients had travelled in the tropics, or practiced watersports of any kind. The route of infection stays thus unclear.

3.7.2. One Health approach in investigating Leptospirosis in the Val Müstair

Since leptospirosis had never been diagnosed in patients of this valley before, the chief doctor of the local small hospital, who discovered the cases, contacted veterinary medicine specialists at the Vetsuisse Faculty, the Institute of Veterinary Bacteriology (IVB) and the Centre for Fish and Wildlife Health (FIWI) in Bern, in order to know if any epidemic among animals had been observed in that region, with potential further spread to humans.

In addition, he contacted the local wildlife guard, to gather information about wildlife in the valley and further potentially infected animals. The answer was that indeed, a few years before, many predators died of an epidemic of distemper. This might have augmented the number of rodents in the region.

At the time of diagnosis of the 3 patients there were no dead animals found in the valley in any suspected way, told the local life guard. Overall feral animals seemed to be healthy.

A rodent specialist and biologist who researched on the rodent population in the Val Müstair and neighboring valleys did not observe any epidemic or susceptibly ill animals, neither did his colleges in that field.

The Institute of Veterinary Bacteriology at the Vetsuisse Faculty in Bern, assessing leptospirosis infection among domestic animals did not report any cases of infected cattle, horse, sheep or pig in this area of the country. The local veterinarian in Müstair diagnosed a case of leptospirosis in a dog from a tourist. He has not observed any infected local animal.

The Centre for Fish and Wildlife Health at the Vetsuisse Faculty in Bern analyzed 3 mice sent to them by the local wildlife guard shortly after the 3 patients were diagnosed with leptospirosis. One of the rodent was positive for leptospirosis. Unfortunately, no MAT could be performed, since not enough blood was available for analysis.

Further 3 healthy foxes were shot by the local wild life guard on request of the FIWI in the setting of a global study aiming to assess the presence and the evolution of leptospirosis among feral animals. This study was performed in Switzerland during 2013 to 2015. Among their results, they observed one serologically leptospirosis-positive fox in the Val Müstair, and a fox with a positive PCR result for leptospirosis in a neighboring valley, Engiadina Bassa. This proves the presence of the pathogen among these feral animals, who could potentially act as reservoir in the disease transmission. Using predators as “sentinel” for monitoring emerging infectious diseases in the environment has been demonstrated to be useful in 2011 in the UK [36].

4. DISCUSSION

4.1. Evolution of Leptospirosis in Switzerland

The evolution of the disease in Switzerland has been categorized in two time groups: one before 1998, and the other after 1998. This corresponds to the decision of the Federal Office of Public Health in 1998 to stop the mandatory notification of leptospirosis in this country. The reasons mentioned were: the little number of cases per year, and this in a steady manner over time [33].

4.1.1. Before 1998

The Federal Office of Public health has kept records of notification by doctors or laboratories from 1988 to 1998.

On this basis, an incidence rate could be calculated, roughly 0,08/100'000 [15], which corresponds to 61 cases collected in these 10 years.

Another calculation is described the article “La leptospirose - une maladie professionnelle” [14]: an incidence of 0,05/100'000/year is calculated for the general population, and its incidence is up to 28x higher among “at-risk” professional groups such as sewage workers, abattoir employees and community workers, with an incidence of

1,4/100'000 population. In farmers and cheese makers an incidence as high as 0,51/100'000 has been measured, thus 8x higher as in the general population.

We didn't have direct access to the above-mentioned data: after contacting the public health authorities, we have obtained a provisory report about the cases collected between 1988 and 1998, a report that has not been published and should not be used as a basis for any sort of interpretation, which is the reason why we will not further discuss it here. This situation highlights the perception of leptospirosis in Switzerland, which is based on a small amount of data and insufficient knowledge.

4.1.2. After 1998

Since leptospirosis was not a notifiable disease any more after 1998, we have searched for other methods to assess the presence of the disease.

Some European countries possess reference laboratories to monitor the evolution of particular diseases. In Switzerland there is a veterinary reference laboratory for leptospirosis that was not meant to provide diagnosis of human cases.

Thus, clinicians will send their samples to different laboratories for human medicine which will further send the samples abroad, depending on the chosen diagnostic test.

ELISA tests can be performed in Switzerland (for instance at the Labor Team W, in the canton of St. Gallen), but PCR and MAT will typically be accomplished abroad (for example: PCR in a fisherman in Geneva was performed in Germany).

The Zentrum für Labormedizin in St. Gallen used to perform MAT for human medicine diagnostics in the past. Nowadays, the difficulty of maintaining a pool of live strains of *Leptospira* spp. for different serovars to complete a MAT outweighed the benefit of performing this test in this laboratory. Thus probes are now sent abroad for diagnostic [62].

Since neither the Federal Office of Public Health nor a central laboratory could give us a reliable overview of the actual situation on human leptospirosis in Switzerland after 1998, we were glad to collect information from the Federal Office of Statistics, who happened to register all hospitalized cases throughout the country.

Yet, this would not allow us to identify any localization of cases, nor provide detail about clinical courses of disease, or even more important: to know if hospitalized cases were contracted abroad or locally.

The help of the infectious disease specialists throughout the country who replied to our questionnaire enables us to localize cases, draw a map of autochthonous infections, and reply to the question: "Is leptospirosis still present in Switzerland after 1998?" The answer is yes.

Year	local	imported	total
2001	1		1
2004	2		2
2008	3		3
2009		1	1
2010	1		1

2012		1	1
2013	7	1	8
2014	5	6	11
total	19	9	28

Table 3 local (68%) and imported (32%), suspected and confirmed cases of leptospirosis diagnosed and treated in Switzerland after 1998.

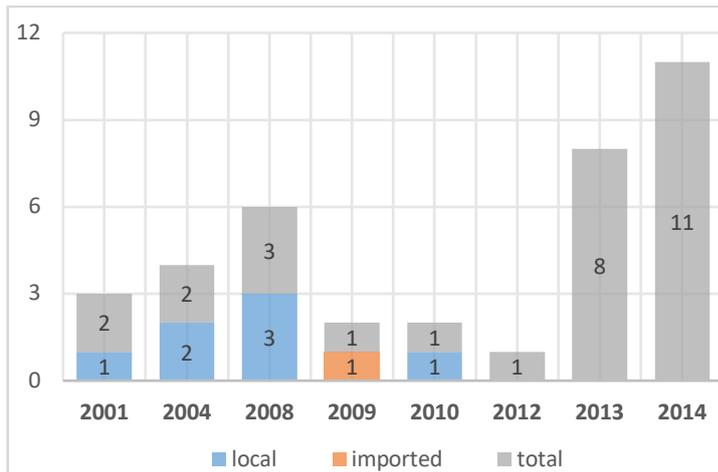


Figure 9 Graphic of autochthonous and imported leptospirosis cases in Switzerland from 2001 until 2014

The increase in the number of cases in 2013 and 2014 is related to the clusters identified in the region of Zürich (3 confirmed cases) and in the Val Müstair (3 suspected cases). Also in 2014, a single family returning from a trip in Thailand got infected (2 confirmed and 2 suspected cases) after swallowing river water while performing river rafting [24]

If we focus only on autochthonous cases in 2013 and 2014, then we have a finding of 7 in 2013 and 5 in 2014, thus in the range or slightly above the mean of 5 cases /year, which was calculated on mixed imported and autochthonous cases.

Unfortunately, it is not possible, based on our current findings, to evaluate the exact evolution of imported vs autochthonous cases.

Yet the overall slight increase of global cases observed in the years 2013 and 2014 can be kept further in mind when we will compare our findings with those arising in other countries.

4.1.3. Evolution of leptospirosis in Switzerland

In an attempt to approach the evolution of the disease, we established a table of cases diagnosed after 1998, and integrated the data from the Federal Office of Public Health (BAG, cases from 1989 to 1989, reports from doctors and laboratories), from the Federal Office of Statistics (BAS, cases from 1999 to 2013, hospitalized cases) and the cases in our study diagnosed after 1998 until 2014 (based on the questionnaire and literature review).

The following graphic appeared:

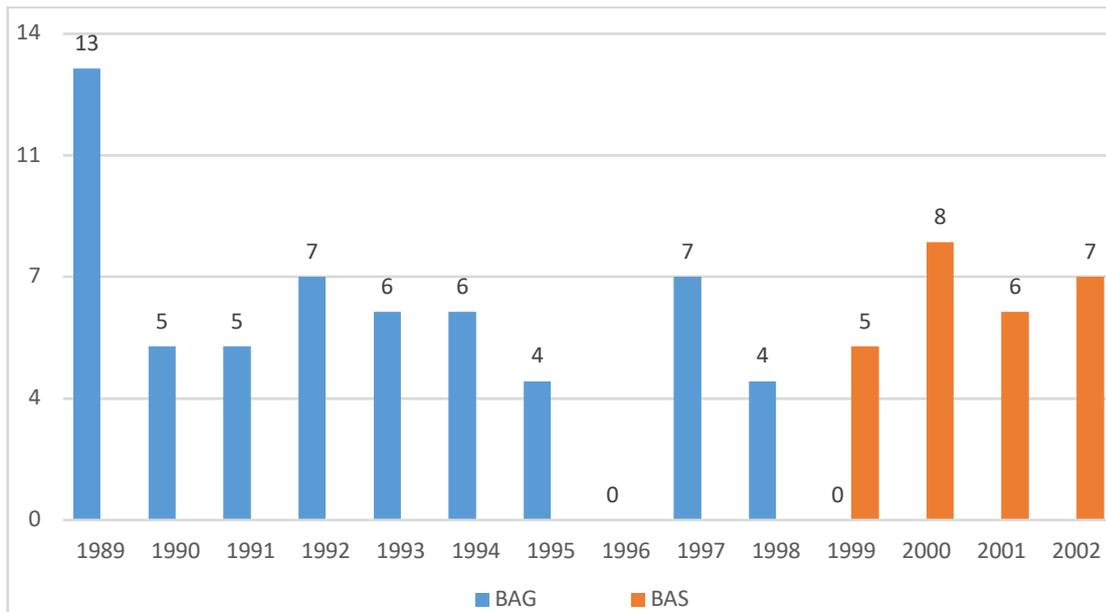


Figure 10 Evolution of human leptospirosis cases (probable or confirmed) in Switzerland from 1989 to 2014

It is impossible to assess the exact evolution of “locally acquired cases”, since only data from our current study distinguish autochthonous from imported cases. The data from BAG and BAS do not make this distinction. Thus the marking “study” also represents both gathered local and imported cases from our study.

In this graphic, the number of cases per year appears to be stable, with roughly a mean incidence of 5 cases/year, even though methods of collecting data differed.

It can be supposed that these numbers underestimate the real prevalence of this disease, since the Federal Office of Statistics mentions only hospitalized cases of leptospirosis. What about those treated in an ambulatory setting? If the severe disease form presents only in 10% of cases, then the above shown numbers might represent only the tip of the iceberg.

In our study, cases treated in ambulatory settings have been considered as well, some of which presented milder symptoms. This might account for the raise in the number of cases seen in the columns 2013 and 2014.

We have mentioned the bias “autochthones vs imported cases”, the same can account for “ambulatory vs hospitalized” as well (BAS mentioning only the hospitalized cases).

Increase in recreational water-activity related infections

Recreational water-activity related infections tend to increasingly be known as potential route of infection of leptospirosis [21, 26-31].

Not only imported cases like the previously mentioned family returning from white-water rafting in Thailand were associated with this route of infection [24], but also increasingly autochthonous cases in Switzerland.

In 2013 and 2014, 4 cases were associated with surfing on the river Reuss [21, 41], and 3 cases associated with professional fishing activities in Geneva.

A local newspaper, the Tribune de Genève even quotes a fisher saying, in 2013, that as much as 5 out of 19 fishermen contracted the disease [63].

In the Swiss literature, bathing in river and lakes has been associated with leptospirosis infection back to 1984 (Geneva) [38] and as early as 1970 in Ticino (4 cases swimming in a lake, one leading to cerebral hemorrhage and death) [42].

In our study, among imported cases from other European countries, a woman got infected while canoeing in France (Drome) in 2014, a man got infected in the Czech Republic while surfing in 2013, and patient in Serbia while bathing in a river before 2000.

In Summer 2006, an outbreak among triathlon athletes has been observed in Germany [64], an on an international level, outbreaks of water-sport related infections have been observed in 2005 in Florida [30], and among triathlon participants in Illinois in 1998 [28].

The awareness of the risk of a leptospirosis infection through recreational water sports has thus certainly been rising in the past years, although the association with recreational activities may still not be well known among physicians, leading to significant underdiagnoses of leptospirosis [21].

4.2. One Health approach: comparing human results with wildlife analysis

The results from our current study on human leptospirosis in Switzerland, alone, would not bring sufficient evidence about the disease in this country, and about the evolution of the disease in this area of Europe.

Hence, we need to consider as well data collected from our colleagues in the veterinarian field, and as well, from other environmental specialists such as wildlife guards and biologists.

In our example of the Val Müstair, knowing that a fox was found having positive antigen for leptospirosis in this valley, and a fox with a positive CRP (thus an active disease carrier) in a neighboring valley, outlines more than just suppositions about the presence of leptospirosis in altitude regions of Switzerland.

A mouse was caught in the center of the valley, and sent by the wildlife guard to the Center for Fish and Wildlife Health at the Vetsuisse Faculty in Bern, in 2014. The positive result for leptospirosis (by CRP in blood), confirmed again the presence of an active disease among animals in this place.

Evidence of an increase of the disease cannot be given based on this little number of cases, and no previous sampling was made before. Yet, we can say: “Yes, it exists.”

Countryside alone has been assessed as a “risk factor” for leptospirosis, thus the link to the human cases that were supposed, can be made, at least, on a “suspected” level. Through evidence provided by animal medicine, the “pre-test probability” of the disease in this zoonosis rises significantly.

Eventually, the presence of positive serologies for Leptospirosis among Capricorns, symbol of “high altitude fauna”, underlines again the possible and obvious presence of leptospirosis in mountain areas in Switzerland.

Note that the incidence of previously mentioned positive foxes found in the area of Val Müstair/ neighboring valley, was not higher than elsewhere in Switzerland. It would be of scientific and public health interest to further assess leptospirosis in humans and in animals in rural and mountain areas in Switzerland. Indeed, outdoor sports are very common, and assessing them as “risk factors” for leptospirosis would rise the attention

of medical practitioners and of the population on a possible transmission of the disease.

4.3. Switzerland in the middle of Europe: comparing results with other countries

In Europe, a variety of strategies for assessing local Leptospirosis can be seen. Some countries have their national laboratory, for instance France, which allows a very precise assessment of evolution and incidence of this disease among the population [12].

Other countries rely on national reporting systems, such as Germany and Austria, and comparing the findings of reports with prevalence studies is interesting:

In Germany, a prevalence of > 0.04 per 100'000 was observed in Baden- Württemberg, bordering Switzerland, based on national surveillance data [53]. When further assessed in a study measuring risk factors for human *Leptospira* seropositivity in South Germany, 42% of 1007 participants were seropositive, showing that seroconversion is much more frequent than commonly assumed on the basis of national reports [55].

Similar findings were observed in Austria, where a positive serological screening result was observed in 23% of 400 healthy individuals tested, much higher than expected based on an annual incidence report of 0.13/100'000 population [65].

In Italy, out of 220 reported locally infected leptospirosis cases between 1994 and 1996, the majority, 83.8% was observed in the northern regions of the country [50]. Even though the exact localization is not described in the study, a proximity to Switzerland, at the northern border of Italy, can be suspected.

It is also interesting to see an epidemiologic trend observed in Germany: after a steady decrease in the disease incidence from 1962 to 1997, a increase was again noted in the years 1998-2003 [53].

In France and in the Netherlands, a significant increase in the number of diagnosed cases in 2013 and 2014 even alarmed public health authorities [12], and encouraged the assessment of leptospirosis in Europe in a study currently conducted by the KIT in Amsterdam [35].

It is interesting for Switzerland too see the parallel made in the Netherlands between the higher incidence rate among dogs, and among humans, rising together [13]. In Switzerland, a recent increase of dog leptospirosis has been observed by the small animal hospital in Bern between 2003 and 2012 [43]. A such parallel with increase in human leptospirosis could be an interesting theme of study, for instance, by assessing the prevalence of the disease among the population.

Eventually, the Center of Disease Control in Stockholm is monitoring the disease among many others. In their report in 2014 covering the years 2008-2012, they did not observe a significant increase in reported cases. In 2012, the annual epidemiological report rated confirmed cases to 0.13 per 100'000 population in EU/EEA, similar to reported rates in 2006-2009 [10].

To date, the actual results of our current study showed an average incidence of 0.08/100'000/year before 1998 without proven increase since then, though with significantly lower incidence than reports in other neighbouring countries. This outlines a potential underestimation of the real incidence of the disease in Switzerland, as we will discuss in a further chapter.

4.4. A specific case-series: leptospirosis in altitude, in the Val Müstair

We have described the three suspected cases of leptospirosis in Mai 2016 in the Val Müstair, which had never occurred before. We have also shown the possibility of the disease among humans, based on veterinarian evidence of disease in this area of Switzerland.

Thus, based on these findings, the pre-test probability of the local population rises significantly.

Furthermore, the cluster of cases diagnosed in Zürich in August 2015 among surfers, showed an active presence of the disease in the country.

Comparing the disease patterns such as clinical signs and symptoms as well as evolution of the disease in these two groups also supports the findings of a positive leptospirosis ELISA test in the three patients in the Val Müstair.

In particular, the quite unspecific symptoms of case n° 2 who complained of headaches and loss of concentration over time, can be paralleled with those of a young female surfer whose main symptoms were headaches of unclear origin.

The typical biphasic evolution of the disease noted in case n°1 and case n°3 also corresponds with the clinical features of leptospirosis described in the literature [1].

Even though no clear route of infection could be found in these three patients, and the status of “suspected cases” remains because of a lack of confirmatory second serology, the suspicion of leptospirosis should be, based on their probable infection, significantly raised among the rural and altitude population as well as tourists who spend outdoor activities in these areas.

4.5. Burden of disease and potential underestimation of a “neglected disease”

The WHO and the GLEAN, as well as many authors, have pointed out leptospirosis as a “neglected disease” [3, 5, 9, 66].

One of the hypothesis is that too little precise, quick and cheap testing is available for the pathogen recognition. Second, the untypical signs and symptoms shown by infected patients render the suspicion of this disease very difficult. Thus, many disease carriers will be diagnosed as flu, pneumonia, headache of unclear origin, gastroenteritis or “some sort of viral infection” in mild cases, and a large differential diagnosis in multiple organ failure such as liver and kidney failure accompanied by coagulopathy. Cerebral and pulmonary hemorrhage due to coagulopathy needs not necessarily to be associated with leptospirosis.

In tropical countries, dengue fever, typhoid fever and malaria can count among differential diagnosis.

Since the variety of signs and symptoms are so unspecific, and diagnosis difficult even with serology testing of PCR in blood or urine, the public health authorities’ attention is more difficult to attain than for other “clear defined” diseases.

In Switzerland similarities exist. The little number of cases diagnosed each year, the variety of clinical signs and symptoms of leptospirosis and the difficulty in assessing specific local serovars responsible for an endemic disease gave to date too little support to preoccupy the public health authorities. Yet, this study should show the presence of endemic leptospirosis in humans in Switzerland, and focus on “at-risk” activities such as surfing, fishing, and perhaps outdoor sports in rural mountain areas.

Leptospirosis should thus not only be tested in clear cases such as returning from a tropical country trip, but also among the local population.

Furthermore, the high incidence among fishers in Geneva should raise the local public authorities' attention on the presence of the disease close to lake borders.

Water-related activities are rich in Switzerland, and other sports such as swimming, wind-surfing and diving could also be assessed as "at-risk" activity.

In the canton of Aargau, in Bremgarten more specifically, we have mentioned 3 infected cases diagnosed in 2014 in Zürich. Another case diagnosed in Luzern might have surfed on the same wave at the same spot.

How many of these surfers might have contracted the disease, and how many further are at risk? On the home page of this municipality, attention to gastro-enteritis and other viral infections is brought to surfers on this well-known wave, but the name leptospirosis is not mentioned.

Eventually, in the canton of Graubünden, leptospirosis is not commonly looked after in the state hospital in Chur, except in the presence of severe liver and kidney disease, says the chief infectious disease specialist. Awareness of endemic leptospirosis in the valleys of this canton is not known, but probably low. The case of 3 probable infected patients in the Val Müstair is related to the knowledge of tropical medicine and clinical patterns of leptospirosis by the chief-doctor of the small hospital in this valley.

Overall, we could reasonably say, similarly to our neighboring searchers on the topic of leptospirosis [32, 55, 65], that this disease is very much likely to be largely underdiagnosed in Switzerland.

The burden of disease is yet not to be underestimated. Patients have undergone a severe disease with high mortality or morbidity scores, dialysis for many months in some cases, and a fatal outcome in two. Not only are liver and kidney failure, myocarditis and coagulopathy signs of severe disease, but it is also their consequences such as multiple organ failure, arrhythmias and hemorrhage leading to need of intensive care support or eventual death in one patient that should rise concerns about this disease among the public health authorities.

Eventually, also milder forms of disease consider attention. Severe or long lasting headaches for which no clear diagnosis can be made, can be, in the absence of other organ injuries such as liver and kidney, if not life threatening but still a significant burden of disease.

Its more typical presentation as a headache or as aseptic meningitis in young woman, in absence of other typical findings, could be a reason of underdiagnosed leptospirosis in this gender, compared to males. The large differential diagnosis of headaches, especially among females, such as tension headaches, migraines etc. could also mask a leptospirosis.

The rapid clinical amelioration of the case two in the Val Müstair is interesting: she had already been given amoxicillin, which should have cured the disease. If her long lasting severe headaches were due to the immunologic response to the pathogen, and not from the pathogen itself, why did she clinically improve rapidly on doxycycline after the laboratory result of a positive serology for leptospirosis was revealed?

It is not the purpose of this study to find an answer to this question, but it is rather the intention to open the hypothesis of the impact of “knowing the diagnosis” on the possibility for a patient to recover from it. Having symptoms that cannot be explained by extensive laboratory and imaging procedures can be an underestimated burden for patients.

If rising awareness on possible local leptospirosis infections among the local population in Switzerland could define a diagnosis in even a very little number cases, of mild and severe diseases, then the work done in the present study will be of significance.

4.6. Global awareness and triggers for detecting disease in humans

To date, the recent creation of the Global Leptospirosis Environmental Action Network (GLEAN) in 2011 in collaboration with WHO not only aims to raise awareness of the disease on an international level, but also to improve diagnostic facilities and strategies to combat acute disease and epidemic for instance in cases of major environmental issues such as flooding [9, 67].

On a European level, the effort is on gathering direct information from different countries by the Royal Tropical Institute Amsterdam (KIT) who is leading a study on that subject. In individual countries, approaches towards leptospirosis diagnosis, awareness and assessment remain very different [68].

In Switzerland, the focus on leptospirosis research in animals is set by veterinarians in different Institutes and Departments of the Vetsuisse Faculty in Bern and Zürich: The Small Animal Clinic, the Institute of Veterinary Bacteriology (IVB) and the Center for Fish and Wildlife Health (FIWI) in Bern and the Epidemiology Section in Zürich. They are concerned by the disease in animals, but also in humans. An interdisciplinary Leptosira symposium was organized by IVB and held in Bern in July 2016, reuniting international and national specialist in veterinary and human medicine, and researchers [61].

In human medicine, colleagues who diagnosed the cluster of three cases among surfers published their findings and presented them on a poster at the joint annual conference of the SGI-SMMI, SSI, SGNOR/SSMUS and SSHH (Swiss Societies of Intensive Medicine, Infectious Diseases, Emergency and Rescue Medicine and Hospital Hygiene) in September 2015 [21, 37].

Further published cases among local and imported leptospirosis help raising the attention to this disease, its patterns and its presence in Switzerland.

General awareness might be “low”, compared to many other rare diseases. When asked about knowledge of the disease, frequent answers among general practitioners or internal medicine specialists in Switzerland are: “1. never heard of!”, “2. Oh, but that is a tropical disease”! 3. “oh, yes, I have heard of a case among “. We have not, in this study, assessed the exact awareness of this disease among colleagues, and aim not to present any numbers.

If known, then the disease is associated with typical occupational exposure, contact with rodents, or water. These are also the most typical routes of infection leading to a diagnosis of leptospirosis.

What about all cases that have not been thought of?

In the cases of the cluster of fishermen in Geneva, 2 out of 3 cases have asked their physician to test for leptospirosis, since they knew the dramatic outcome this disease may have after a severe clinical evolution in one of their colleagues.

Two of three surfers in the cluster published by infectious disease specialists in Zürich were also suspected after the diagnosis has been made in one of them.

The same evolution in the Val Müstair: after a first diagnosis was made in a patient, prompt searching for disease was made in two other, resulting in rapid treatment and complete recovery in an 88-year-old who might have sustained a potentially severe disease, based on her age, if not treated rapidly.

Overall, on an international and national level, the awareness of water-related activities and recreational outdoor activities is raising after triathlon epidemics were described in Nicaragua, USA and Germany. On a national level, after publication of 4 surfer cases in 2014 and 2015 (1 in Luzern and 3 in Zürich), this route of infection also appears to be “at-risk”. The publication of a family returning from whitewater rafting in Thailand and diagnosed with leptospirosis in Lausanne underlines this process.

We highly recommend to consider leptospirosis in the differential diagnosis of flu-like symptoms associated or not with headaches and/or signs of abnormal liver, kidney and coagulation function on laboratory results, especially if water-related exposure is suspected or other classical exposure routes such as farming, occupational sewage workers, etc.

It is a potentially largely underestimated disease, even in Switzerland, and its investigation could be worthwhile in ICU patients presenting multiple organ failure and/or severe hemorrhages of unclear origin. It could also enter the differential diagnosis of myocarditis and aseptic meningitis.

The development of new diagnostic technologies would aid this process.

5. CONCLUSIONS

5.1. Leptospirosis in Switzerland: a potentially fatal, probably underestimated and underdiagnosed disease of possible local and global importance

Assessing the presence of leptospirosis and its evolution over time was done based on the findings of the Ministry of Public Health until 1998, and through a questionnaire sent out to infectious disease specialists in Switzerland in 2014.

If the disease is not notifiable any more since 1998, owing to the fact that a too small number of cases per year were reported and a too small number of fatal cases, it remains, even after 1998, an endemic disease.

Its pattern of disease equals that of leptospirosis acquired abroad. Serovars might be slightly different, yet this was not assessed in the current study. Icterohaemorrhagiae, known to be one of the most virulent pathogen, is also present in Switzerland, and has infected, for instance, a fisherman in Geneva, leading to very high morbidity in this patient. Due to intensive care including hemofiltration and plasma exchange, he survived, which was not the case of two former cases who died of sequels of this disease known to be a fatal in 10% of the cases worldwide.

It should be considered in the differential diagnosis of all fevers with liver and kidney injuries, but also with pulmonary or cerebral hemorrhage or coagulopathy in general.

In a milder disease form, it can mimic a simple flu, and severe headaches can be mistaken for migraines or tension headaches. Aseptic meningitis has been found more often in young women and is also a pattern of leptospirosis.

The mildest forms can be unrecognized; they present themselves with light muscle aches and little headaches and abdominal pain. In some patients, the diagnosis might be found on serology, or PCR in blood or urine. The MAT will eventually confirm which pathogen serovar is implicated. In some patients, the diagnosis might be missed even if these tests were made.

Thus, it remains a very difficult disease to diagnose, through its unspecific clinical features and difficult laboratory tests.

Yet, it is present throughout Switzerland, even if only as little as about 5 cases/year are diagnosed in this country. Specific locations bordering lakes and rivers are at higher risk, and as for other countries, contact with rodents and occupational risk factors are the same. Worldwide, but also in Switzerland, recreational water-related activities are increasingly seen to be risk-factors for leptospirosis infection. We thus recommend medical practitioners to pay attention to this route of acquisition of the disease. This could also include swimmers in lake and rivers, sailors and divers, even if this last-mentioned category of people have not been assessed in this study.

Fishermen have accounted for 10% of our 31 cases, surfers for 13%, swimmers in lake and river for 16%, contact with live rodent for 19%, with rodent excrements for 19%, and altitude and nature for 10%. Remain 16% in other categories.

A particular attention was brought in this study to a rural population and three suspected cases in the Val Müstair. These cases draw the attention to potential infection in altitude and colder areas. Going beyond the well-known “tropical” origin of the disease, mountain and even arctic regions have shown to be hosts for the leptospire, as suggested in literature.

Eventually, the importance of awareness of the disease, and attention brought towards studies and findings in veterinarian medicine and in neighboring countries is outlined in this study.

In neighboring France, incidence raised from as high as 0.43/100'000 to 0.98/100'000 in 2014 [12]. In dogs in Switzerland, an increase in canine leptospirosis was observed over 10 years with a peak incidence of 28.1 diagnosed cases /100'000 dogs/year [43]. In the Netherlands, the observation of a rise in human and animal cases alerted public health authorities' views and supported the hypothesis of an increased environmental exposure in this country [13]. The number of 0.08/100'000 in Switzerland's human cases appears extremely low compared to neighboring and other European countries. The increase in canine leptospirosis in Switzerland could reflect an increase in environmental exposure and could be further assessed.

We thus recommend further research on this topic in Switzerland, and notification of this disease by Public Health authorities.

If no significant rise can be found in coming years, but the disease was notifiable, it can then always be taken back to “not notifiable disease” again.

If a significant effort is made in informing medical staff about the presence of leptospirosis in humans in Switzerland, throughout the country, from lake shores to mountain regions, and the disease is notified, and a significant increase in number of detected

cases and treated patients is found, then the effort of this study and of the public health authorities will have been of great value.

Neighbouring countries, WHO and GLEAN and maybe many other institutions work intensively on raising the awareness of the disease and finding strategies including better diagnostic methods to combat this known to be an “emerging disease” worldwide.

Yet this study could not show a rise in number of cases per year in Switzerland, we recommend to draw the attention to new diagnostic methods and literature on this emerging subject. The Vetsuisse Faculty and national reference laboratory for animal leptospirosis in Switzerland (the Institute of Veterinary Bacteriology) proposed to diagnose *Leptospira* serovars in humans based on MAT method, for research and scientific purposes. If the public health authorities reject the present proposition to make leptospirosis a notifiable disease, this could then be a meaningful possibility of assessing disease in Switzerland.

Vaccines exist in France and in other countries for specific serovars. Knowing which serovars circulate in Switzerland would help to reassess the pertinence of its introduction in Switzerland.

5.2. Outputs

We highly recommend to the public health authorities to pay attention to leptospirosis infection in humans in Switzerland, and its possibility of an emerging pattern.

Indeed, findings in this study suggest that leptospirosis infections are possible in all regions, including lakes, rivers and mountain areas, in addition to the known risk factors of occupational activity-acquired leptospirosis. Neighbouring countries who closely monitor the disease such as France and the Netherlands consider leptospirosis as an “emerging disease”. Furthermore, South-German, Austrian and Italian studies show that the prevalence of the disease might be much higher in humans than expected based on declared /diagnosed cases. Eventually, the possible severe and mortal outcome of locally acquired leptospirosis infections alone invites to draw special attention to this disease.

Overall, even if leptospirosis would not appear to be emerging in the coming years, the number of infected patients might still be much higher as diagnosed and suspected.

We thus also recommend increased awareness on local routes of infections, not only among public health authorities of the different regions in Switzerland, but also among general practitioners, internal medicine and intensive care specialists, together with infectious disease specialists.

In particular, attention should be drawn on the possibility of the disease among swimmers in lakes and rivers, and on related activities.

In order to assess the exact prevalence among this “at-risk” population, further studies are warranted. This could lead to public health prevention panels or specific information given in these groups.

Eventually, since the possibility of locally acquired leptospirosis in rural mountain areas is shown in this study, a further research assessing the prevalence of the disease in this particular group, for instance in the Val Müstair, or other rural/altitude regions

in Switzerland could bring scientific evidence of what we can only propose as “potential risk-factors” in the current work.

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8. APPENDICES

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on following pages:

8.3. Excel tables of autochthonous Swiss cases

8.4. Map of human cases in Switzerland

8.5. Letter to infectious disease specialists (German and French)

8.6. Leptospira Symposium in Bern, 8.7.2016

App. 2a : Diagnosis of collected cases of human leptospirosis acquired in Switzerland since 1970 until 2015

N°	Canton	Age	Sex	Location of infection	Date of Dx	Infection route	Status (C=confirmed)	Serovar	Source
1	GE	29	M	Hermance	6.2013	fishing	C by PCR blood + urine		HUG
2	GE	65	M	Geneva	9.2008	fishing	C by MAT	L. icterohaemorrhagiae	lit. Bourquin
3	GE	62	M	Geneva	11.2008	fishing	C		HUG
4	GE	36	M	Geneva	<2004	sew age worker	C by MAT	L. grippityphosa	lit. Bessire
5	GE	60	M	Geneva	1984	bathing in river			lit. Jacques MC
6	VD		M	Morges	2.2014	rodent on boat	C by serology		CHUV
7	VD		M	Lausanne	2.2014	rat excrements	C by PCR blood + urine		CHUV
8	VD	56	M	(CHUV)	2010	rat bite	C by MAT	L. icterohaemorrhagiae	Lit. Guileri
9	VD	73	M	(CHUV)	2001	plastic swimmingpool	C by MAT	L. australis	Lit. Pantet
10	VD	53	M	Yverdon-les Bains	8.2008	dead rat	C by PCR blood		EHNV
11	VD	63	F	Yverdon-les-Bains	7.2007	horse owner	C by MAT		EHNV
12	VD			CHUV	2010	pet mouse			CHUV (Dr.Oriol)
13	BS	25	F	Basel	2008	rat owner (pet)			USB
14	BS	37	M	Basel	1997	dog urine contact	C by MAT	L. grippityphosa + hardjō	Lit. Stephen
15	BS	71	F	Basel		unknown	C by MAT	L. australis +bratislava	Lit. Stephen
16	ZH /AG	33	M	Bremgarten, AG	10.2014	surfing on river	C by MAT	L. grippityphosa	Triemli Spital
17	ZH /AG	32	F	Bremgarten, AG	9.2014	surfing on river	C by MAT	L. grippityphosa	Triemli Spital
18	ZH /AG	34	M	Bremgarten, AG	8.2014	surfing on river	C by MAT	L. grippityphosa	Lit. Schreiber
19	ZH	66	M		5.2013	bite from dormouse	C by serology		Waidspital
20	LU	28	M	Reuss	2013	surfing on river	C by serology		Lit. Staudenmann
21	GR	60	M	Val Müstair	5.2013	unknown	P (1 serology)		CSVM
22	GR	27	F	Val Müstair	5.2013	unknown	P (1 serology)		CSVM
23	GR	88	F	Val Müstair	5.2013	unknown	P (1 serology)		CSVM
24	TI /GR	38	M	Bellinzona/ Mesocco	8.2013	fishery /farm	C by PCR urine + serology		Francioli
25	TI /GR	59	M	Lugano/ Lake Mesocco		rat excrements on boat	C by MAT	L. canicola	Lit. Bernasconi
26	TI	66	M	Lugano	2000	rabbit breeds/farming	C by MAT	L. icterohaemorrhagiae	Lit. Bernasconi
27	TI	60	M	Lugano	2000	rabbit breeder	C by MAT	L. icterohaemorrhagiae	Lit. Bernasconi
28	TI			Lake Muzzano	early 1970	swimming in lake			Lit. Bernasconi
29	TI			Lake Muzzano	early 1970	swimming in lake			Lit. Bernasconi
30	TI			Lake Muzzano	early 1970	swimming in lake			Lit. Bernasconi
31	TI			Lake Muzzano	early 1970	swimming in lake			Lit. Bernasconi

HUG : Hôpitaux Universitaires Genevois, CHUV: Centre Hospitalier Universitaire Vaudois, EHNV : Etablissement Hospitalier Nord Vaudois
CSVM : Center da Sanda Val Müsair, USB : Universitätsspital Basel

Dx= Diagnosis, C= confirmed, P= probable

Lit. = Literature

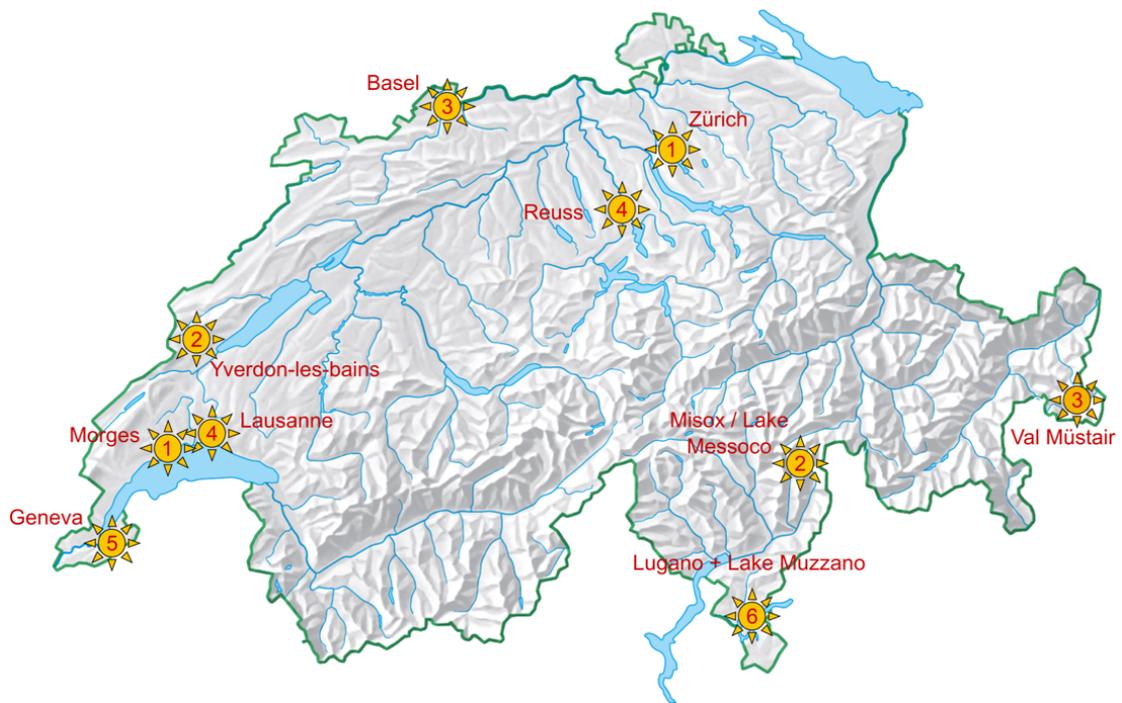
App 2b: Clinical course of disease in collected cases of human Leptospirosis acquired in Switzerland since 1970 until 2015

N°	Canton	Age	Sex	Infection route	Main symptoms/signs	complications	treatment	outcome
1	GE	29 M	M	fishing	F, H, My, arthralgia, conjunctivitis	ELE, ARF, J-Hx	intermediate care	good
2	GE	65 M	M	fishing	F, My, epigastric pain + icterus	ELE, ARF, Th, arrhythmias, sepsis, MOF	ICU + MOF*	good
3	GE	62 M	M	fishing	unknown	unknown	ICU ?	good
4	GE	36 M	M	sewage worker	F, chills, vomiting, severe H	aseptic meningitis, slight ELE + bili		good
5	GE	60 M	M	bathing in river	F, My, arthralgia	coagulopathy, myocarditis		death
6	VD	M	M	rodent on boat	unknown	ARF, dialysis		good
7	VD	M	M	rat excrements	initial mild symptoms, later: thoracic pain	myocarditis, ARF, hepatitis		good
8	VD	56 M	M	rat bite	F, My, Ab, diarrhoea	slight ELE, Th, ARF		good
9	VD	73 M	M	plastic swimmingpool	F, Ma, dizziness	ARF		good
10	VD	53 M	M	dead rat	F, conjunctivitis	ELE, slight elevation of creatinin, J-Hx		good
11	VD	63 F	F	horse owner	unknown	septic shock, ARF, ELE	ICU	good
12	VD		F	pet mouse	unknown	unknown		good
13	BS	25 F	F	rat owner (pet)	unknown	unknown		good
14	BS	37 M	M	dog urine contact	My, H, nausea + vomiting/icteric	ARF, Th, bilirubinemia	Dialysis	good
15	BS	71 F	F	unknown	F, My, Ma, dyspnea	ARF, Th, sepsis, pulmonary haemorrhage	ICU	good
16	ZH /AG	33 M	M	surfing on river	F, H, My	unknown		good
17	ZH /AG	32 F	F	surfing on river	F, severe H, My, meningitis signs	relapse of H and Ma after initial improval		good
18	ZH /AG	34 M	M	surfing on river	F, H, My	ARF, ELE, PANC,		good
19	ZH	66 M	M	bite from dormouse	F, severe H, strong My,	ARF, probable J-Hx	Dialysis	good
20	LU	28 M	M	surfing on river	F, Ma, My, chills, severe H, arthralgia	ARF, ELE		good
21	GR	60 M	M	unknown, countryside	Ma, Ab, diarrhea, night sweats	elevated CRP: 212		chronic illness
22	GR	27 F	F	unknown, countryside	F, Ma, headaches, earache	slight ELE, otherwise normal		good
23	GR	88 F	F	unknown, countryside	F, cough, night sweats	slight ELE, otherwise normal		good
24	TI /GR	38 M	M	fishery /farm	F, dysuria, My, rash	septic shock, interstitial pneumonia	ICU?	good
25	TI /GR	59 M	M	rat excrements on boat	F, My, Ma /icteric, petechiae	ARF, J-Hx, Th	Dialysis	good
26	TI	66 M	M	rabbit breeds/farming	F, Ma, H, /icteric, petechiae	ARF, Th	Dialysis	good
27	TI	60 M	M	rabbit breeder	Ma, vomiting, diarrhoea/icteric	Th, bili, intrahepatic cholestase		good
28	TI			swimming in lake	unknown	ARF, sever Th, cerebral hemorrhage		death
29	TI			swimming in lake	unknown	unknown		good
30	TI			swimming in lake	unknown	unknown		good
31	TI			swimming in lake	unknown	unknown		good

* MOF : multiple-organe failure , ICU treatment for 45 days, incl. Plasma exchange and high-volume hemofiltration, 70 days hospital care

F = fever, H= headache, Ab: abdominal pain, ARF= acute renal failure, Th/PANC= Thrombo /pancytopenia
 Ma= Malaise, My= Myalgias
 ELE= elevated liver enzymes, J-Hx: jarish-Herxheimer reaction

ICU: intensive care unit





Zürich, 13. Oktober 2014

Leptospirose: Informationsanfrage

Sehr geehrte Kollegen und Kolleginnen,

Letztes Jahr gab es in Einwohnern des Münstertals im Kanton Graubünden drei Verdachtsfälle von Leptospirose mit positiven Serologien und unspezifischen Symptomen (Fieber, Muskelschmerzen, Kopfschmerzen, Husten). Diese Verdachtsfälle sind erstaunlich, da Leptospirose im Tal und in dieser gebirgigen Umgebung generell unbekannt ist. Jedoch wurden im Tal 3 Mäuse eingefangen und zur Analyse an das Zentrum für Fisch- und Wildtiermedizin der Universität Bern gesandt wovon eine Maus positiv auf Leptospirose getestet wurde.

Gleichzeitig zeigt sich weltweit ein vermehrtes Auftreten der Leptospirose, welche normalerweise in tropischen Ländern und Regionen mit extremen Klimabedingungen wie Überschwemmungen auftritt. Die steigende Prävalenz lässt sich jedoch auch in gemässigten Klimaregionen beobachten, insbesondere im Zusammenhang mit Wassersportarten wie Schwimmen und River Rafting.

Eine Studie hat eine 10 bis 12-prozentige Seroprävalenz nachgewiesen in Bauern und Förstern nachgewiesen, die in den nordöstlichen Alpen leben (Faine, 1994; Vijayachari, 2008). Dies weist darauf hin, dass das Bakterium auch im Gebirge auftritt.

Wir stellen uns deshalb folgende Fragen:

- Wie sieht es in anderen Schweizer Kantonen aus?
- Genügt eine einzige positive Serologie um die Krankheit zu diagnostizieren?
- Wenn ja, welches wäre die Infektionsquelle bei den drei genannten Patienten? Mit Nagern oder anderen Säugetieren als Reservoir?
- Werden in der Schweiz andere diagnostische Methoden wie die PCR mit Blut- oder Urinproben durchgeführt?

Im Jahr 2010 wurden in der Aareregion drei tote infizierte Biber gefunden und auch bei Hunden wurde in letzter Zeit ein Anstieg der Fälle in der Schweiz festgestellt («Leptospirosis in European Beavers (Castor fiber) from Switzerland», Giovannini et coll., 2012). Zurzeit wird am Zentrum für Fisch- und Wildtiermedizin der Universität Bern (Dr. med. vet. Nelson Marreros und PD Dr. med. vet. Marie-Pierre Ryser) eine Studie zu Leptospirose in Wildtieren durchgeführt.



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Da die Krankheit nicht meldepflichtig ist, sind die Daten zur Prävalenz im Menschen unklar.

Wir fragen Sie deshalb höflich an, ob Sie in den letzten Jahren Fälle von Leptospirose beobachtet haben und wo sich diese infiziert haben könnten.

Wir bedanken uns bestens für Ihre Mitarbeit an diesem Dissertationsprojekt und verbleiben

mit freundlichen Grüßen

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Zurich, le 13 octobre 2014

Leptospirose: Demande d'information

Chers Collègues,

L'an passé, nous avons suspecté trois cas de leptospirose (sérologies positives, forme anictérique avec symptômes non spécifiques [fièvre, myalgies, céphalées, toux]) chez des habitants du Münstertal, aux Grisons. Ces trois personnes n'ont pas voyagé en dehors de la vallée. Cela semble étrange, car ce n'est pas du tout connu dans cette région montagnarde. En même temps, trois souris ont été attrapées et envoyées au Centre pour la Médecine des Poissons et des Animaux sauvages à Berne. Une souris était positive pour la leptospirose.

La maladie semble en émergence dans le monde entier, normalement attribué aux régions tropicales et conditions climatiques extrêmes comme des inondations et cyclones, mais également dans les régions tempérées, notamment chez des pratiquants de sports en relation avec l'eau (nageurs dans les lacs, rafting, etc.).

Une étude italienne a montré une séroprévalence de 10 à 12% chez des paysans et forestiers dans le nord-est des Alpes italiennes (Faine, 1994; Vijayachari, 2008), ce qui montre que la bactérie est bel et bien présente également en altitude.

Nous nous posons actuellement les questions suivantes:

- Qu'en est-il dans les autres cantons suisses ?
- Une seule sérologie est-elle suffisante pour poser le diagnostic ?
- Si oui, quelle serait la source d'infection de ces trois patients ? Rongeurs ou autres mammifères comme réservoir ?
- D'autres méthodes diagnostiques comme la PCR sanguine ou urinaire sont-elles utilisées en Suisse ?

Trois cas de castors infectés ont eu lieu en 2010 dans la région de l'Aare et la leptospirose est en augmentation importante chez les chiens en Suisse (« Leptospirosis in European Beavers (Castor fiber) from Switzerland », Giovannini et coll., 2012). Une étude est actuellement en cours concernant



la faune sauvage (par Dr. med. vet. Nelson Marreros et PD Dr. med. vet. Marie-Pierre Ryser, au Centre pour la Médecine des Poissons et des Animaux sauvages (FIWI), Université de Bern).

Pour les humains, il n'y a pas de données claires, car la maladie ne doit pas obligatoirement être déclarée.

C'est pour cette raison que nous souhaiterions vous demander si vous avez observé des cas de leptospirose ces dernières années, quelles méthodes diagnostiques vous avez utilisées, et où les patients se seraient infectés.

Nous vous serions très reconnaissant de nous communiquer vos cas, à des fins d'étude, en vous assurant tous les respects concernant la confidentialité et la collégialité. Nous serions heureux d'une réponse de votre part, même si vous n'avez pas observé de cas de leptospirose dans votre région.

Avec nos remerciements sincères,

Prof. Dr. med. Christoph Hatz
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**Interdisciplinary
Leptospira Symposium**
Friday July 8th, 2016

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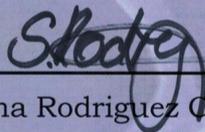
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We hereby certify that

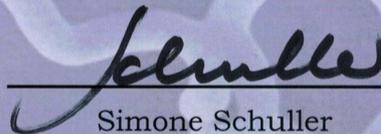
Gwendoline Fiechter

presented a talk with the title

**Leptospirosis in Humans in
Switzerland: Emerging Disease or
Emerging Awareness ?**



Sabrina Rodriguez Campos



Simone Schuller

Vetsuisse Faculty Bern

Länggassstrasse 122, Hörsaal Paraklinik 3rd floor

Supported by the Fund for the Promotion of Young Researchers of the University of Bern

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Interdisciplinary *Leptospira* Symposium

Friday July 8th, 2016

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- 13:30** **Welcome.** Sabrina Rodriguez Campos, Simone Schuller
- 13:35 – 14:20** **Leptospire: Back to Basics – Culture and Models.** Jarlath Nally, National Animal Disease Center-USDA-ARS, Ames (IA), USA
- 14:20 – 14:35** **Epidemiology of Leptospirosis in Switzerland: first insights into the wildlife side.** Nelson Marreros Canales, Centre for Fish and Wildlife Health, Vetsuisse Faculty Bern, CH
- 14:35 – 14:50** **Leptospirosis in Abortion in Ruminants – a myth?** Sara Vidal, Institute of Veterinary Bacteriology, Vetsuisse Faculty Bern, CH
- 14:50-15:05** **Inflammation and Coagulation in Canine Leptospirosis.** Thierry Francey, Small Animal Internal Medicine, Vetsuisse Faculty Bern, CH
- 15:05 – 15:20** **Leptospirosis in Horses in Switzerland.** Stefanie Gobeli Brawand, Institute of Veterinary Bacteriology, Vetsuisse Faculty Bern, CH
- 15:20 – 15:50** **Coffee break**
- 15:50 – 16:20** **Diagnostic Tests for Human Leptospirosis.** Marga Goris, Royal Tropical Institute Amsterdam, NL
- 16:20 – 16:35** **Leptospirosis in Humans in Switzerland: Emerging Disease or Emerging Awareness?** Gwendoline Fiechter, Spital Linth, Uznach, CH
- 16:35 – 16:50** **Endothelial cell responses to pathogenic *Leptospira* spp.** Sophie Lettry, Small Animal Clinic and Institute of Animal Pathology, Vetsuisse Faculty Bern, CH
- 16:50 – 17:05** ***Leptospira* Seroprevalence in Health Centre Patients in Hoima District, Uganda.** Anou Dreyfus, Epidemiology Section, Vetsuisse Faculty Zurich, CH
- 17:05 – 17:20** **Discussion and closing remarks followed by a reception.**

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Please register by e-mail to ivb.lepto@vetsuisse.unibe.ch

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