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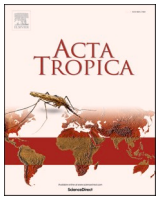

Rabies control and elimination in West and Central Africa

The reports in this *Special Issue* of Acta Tropica 2021 "Towards the elimination of dog rabies in West and Central Africa" contribute to the "One Health" framework – with the exception of the Pakistani articles - to assess rabies burden and vaccine demand in West and Central Africa and to plan implementation of the "Rabies Vaccine Investment Strategy" (VIS), funded by Gavi (the Vaccine Alliance, previously the Global Alliance for Vaccines and Immunization). Gavi initially funded the estimation of the burden of rabies in Côte d'Ivoire, Mali and Chad, work which produced most of the articles assembled here. The "One Health" approach demonstrates an incremental benefit or an added value of a closer cooperation between human and animal health and any related environmental or social sciences. (Zinsstag, 2020, 2021).

The *Special Issue* features a broad range of African partners and their institutions, which are depicted as a wordle in Fig. 1. The high levels of connection between Direction des Services Vétérinaires in Côte d'Ivoire, Laboratoire Central Vétérinaire in Mali, Centre de Support en Santé International in Chad and the Swiss partners are notable.

Reviewing the abstracts of the *Special Issue*, in addition to the obvious terms rabies and dog, the key words (post) exposure prophylaxis or its abbreviation PEP, bite victims, exposed people, human rabies, rabies center, and rabies control (program) are the most relevant terms addressed, as shown in Fig. 2.

The Special issues begins with *"Dog rabies control in West and Central Africa (Review)"*, summarizing the current rabies status in 22 West and Central African countries by (Mbilo et al., 2020). The review considered all available scientific publications and data from national rabies authorities and scientists. This information is valuable to plan the next steps on the way to total elimination of the disease in Africa. Their findings show that most of the countries still struggle with financial limitations and lack of government engagement. International support and regional cooperation are urgently needed to reach the common goal. They present different networks with this target, including the Pan-African Rabies Control Network (PARACON), and international resources available for affected countries. At the outset, dog rabies control and elimination is clearly an issue of political will to cooperate and invest nationally and at the regional level.

1. Epidemiology

The paper "*Increasing rabies data availability: The example of a One Health research project in Chad, Côte d'Ivoire and Mali*" by (Lechenne et al., 2021) anchors this *Special Issue* by describing the implementation of a project funded by the Vaccine Alliance (Gavi). It evaluates success with regard to information gained, capacity building achieved, impact on knowledge creation and influence on national and international policies. The project was based on the One Health concept and guided by the principles of transboundary research partnerships formulated by the Swiss Academy of Sciences.

In most cases, rabies is dog-mediated, as shown by Traore et al. (2020) in the article "*Rabies surveillance-response in Mali in the past 18 years and requirements for the future*", with about 95% of rabies cases in Mali caused by dogs. Virus transmission occurs via contaminated saliva, mostly through a bite or skin lesion. Consumption of dogs for food, a traditional habit in some communities, brings an additional risk of rabies infection for dog owners, hunters and butchers. Symptoms in humans and animals are the result of acute encephalitis and lead to either a furious or a paralytic form of rabies. Depending on the location of infection and viral load, the incubation time varies from a few days to several months, whereby the closer to the central nervous system the bite occurs, the faster the symptoms begin and become fatal. The earlier the case is diagnosed, the better for control success. Rabies lyssavirus causes about 59,000 human deaths per year worldwide, mostly in low and middle income countries (LMICs) where the majority of the victims are children, who usually have closer contact with dogs.

Human rabies is a significant public health concern in Tunisia. New results show that roads and irrigated areas can act as ecological corridors to viral spread. There seems to be a significant seasonal variation in the cases of rabies recorded, with a strong peak in spring and lower peaks in winter and summer (Hassine et al., 2021).

"*Rabies knowledge and practices among human and veterinary health workers in Chad*" by Mbaipago et al. (2020b) is foundational to the wide-scale study on the burden of rabies and vaccine demand in Chad. The goal was to assess the basic knowledge and practices of health staff about rabies with questionnaires before and after a one-day intensive training. The findings clearly point to lack of information about rabies in veterinary and human health workers' education in Chad. They call for improved long-term professional training under a One Health approach to fill these gaps in expertise.

2. Risk factors

Rabies is not a legally notifiable disease in Chad, therefore official national surveillance data is not available which makes it challenging to point out the importance of rabies medical care to the authorities. "*Identification of risk factors for rabies exposure and access to post-exposure prophylaxis in Chad*" by Madjadinan et al. (2020) increases awareness using evidence collected in a representative cross-sectional household survey and through a 20-month bite incidence survey in public health facilities. The participating human health workers were previously trained in the workshop noted earlier by Mbaipago et al (2020b). The

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Fig. 1. Depiction of partners, weighted by frequency of institution name across all papers in this *Special Issue*

project provided free of charge human rabies vaccine for PEP to hospitals and health centers in the region. PEP was based on active immunization only, as human derived rabies immunoglobulin (RIG) was not available in Chad.

Household surveys reported that only 33% of bite victims sought help at a medical facility, including pharmacies. Alarmingly, only 8.5% of cases could obtain access to human vaccines. The lack of a functional cold chain is a major problem for remote health facilities. However, even if the closest health center had vaccine in stock, the amount charged for PEP was not affordable for most Chadians. Key risk factors for rabies virus infection were dog bites, owning unvaccinated dogs and seeking health care from a traditional healer. The main risk factor for dog bite exposure was being of Christian religion as Muslim households own dogs considerably less often.

Madjadinan et al. (2020) found that only 4% of dogs in urban and 1% in rural areas were vaccinated against rabies. Reasons for non-immunization included lack of awareness of the need for vaccination or the place to find it and lack of financial means. Chad is still is confronted with numerous challenges in the fight against dog rabies, but the data presented here helps face these challenges and assist to plan future strategies.

A similar household survey was conducted in Côte d'Ivoire, where public health stakeholders defined rabies as a priority zoonosis in 2017. With "*Estimation of dog population and dog bite risk factors in departments of San Pedro and Bouake in Côte d'Ivoire*", Kallo et al. (2020) publish important data for implementation of a national control strategy. On average, the local population owned one dog per three households which allowed for an estimate of 1,400,654 dogs in 2016. This number is 15 times higher than the numbers noted by official services (OIE, 2012). This is the first time a study of the dog population size in Côte d'Ivoire was undertaken, revealing that about 80% of dogs lived in rural areas. The overall rabies vaccination coverage was only about 12%, only half of which were confirmed with vaccination cards. About 40% (60%) of bite victims were female (male), thus, the main dog bite risk factors were being male and owning a dog. The authors emphasize the importance of a future study to estimate more precisely the number of stray dogs in Côte d'Ivoire.

Risks for human rabies in Côte d'Ivoire point towards the geographical accessibility of anti-rabies centers, many non-completions of rabies PEP in the context of ignorance. Establishment of a national comprehensive integrated rabies control program is needed in Côte d'Ivoire. It must take into account these factors and focus on public awareness, dog vaccination and adoption of modern intradermal vaccination regimens to better manage the rabies situation in Côte d'Ivoire (Tetchi et al., 2020b).

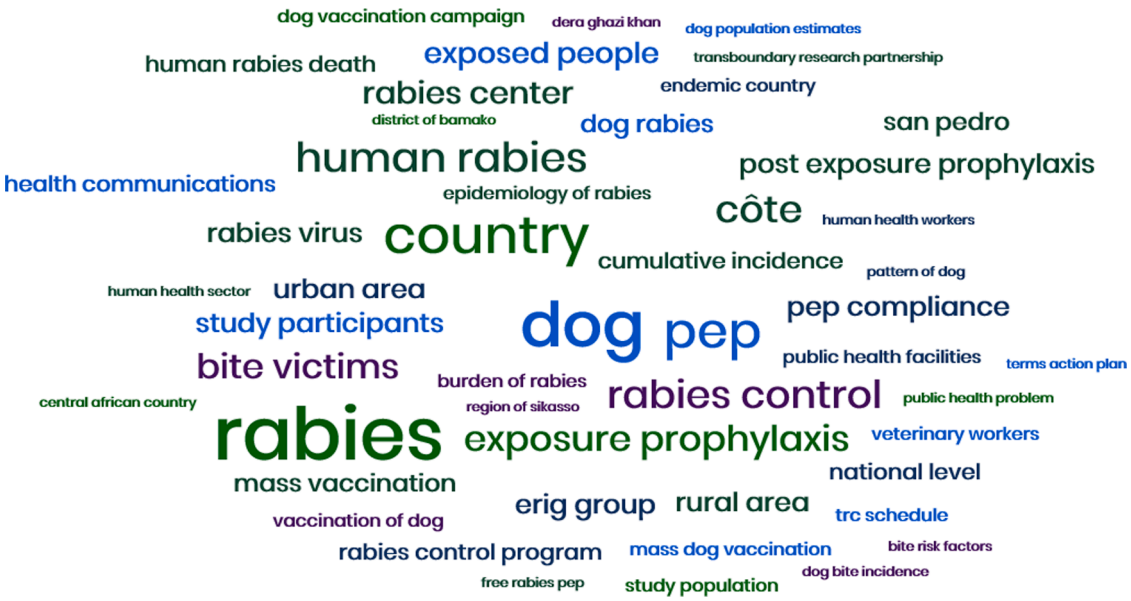

Fig. 2. Key word frequencies in the abstracts included in this *Special Issue*. (PEP = post-exposure prophylaxis).

3. Burden of disease

Keita et al. (2020) show in the article "*Burden of rabies in Mali"* that in 2016 and 2017 a total of 269 people died of rabies in the country, with a loss of income estimated at 6.5 million USD. They reference Hampson et al. (2015) who found that sub-Saharan African countries have the highest *per capita* mortality. Every country on the African mainland is considered endemic for this disease.

Using the same approach as Keita et al. (2020), the "Burden of rabies in Côte d'Ivoire" by (Kallo et al., 2021). estimates the number of 637 deaths from rabies per year. This number translates into a human mortality from rabies of 2.61 per 100'000 people, which represents 24-47 times more cases than the official data. The annual cost of rabies is estimated at 40 million USD, of which 99% was due to premature death. This study highlights the underreporting of rabies cases by the official health information system in Côte d'Ivoire. The annual financial loss is equivalent to the cost of elimination of rabies by 2030.

In summary, the contributions to this *Special Issue* show that rabies continues to be a serious problem, although the disease is 100% preventable with the right treatment using the very effective dog and human vaccines and PEP that already exist on the market. Human PEP consists of active vaccination and the use of immunoglobulins to prevent human rabies after the exposure to a suspected rabid animal bite (World Health Organization, 2018a. It is estimated that worldwide over 15 million people a year should receive PEP after exposure, but it is often not accessible in LMICs.

The Global Strategic Plan for collaboration between the World Health Organization (WHO), 2018b, the *World Organisation for Animal Health* (OIE), the *Food and Agricultural Organization of the United Nations* (FAO), the *Global Alliance for Rabies Control* (GARC), and the *United Against Rabies* collaboration, aims to eliminate canine-mediated human rabies by 2030 (World Health Organization, 2018c). In theory, this goal is achievable as it is proven that rabies can be eradicated with mass dog vaccination. However, the most affected countries still face many challenges on the way to eliminate rabies, as the studies in this *Special Issue* reveal. Even worse, the actual incidence of human rabies cases in Africa is likely to be 100 -160 times higher than official records (Cleaveland et al., 2002; Mauti, 2019). This is due to poor disease surveillance, as bite victims often do not have the means to visit a medical facility and most cases are not confirmed by a laboratory or are simply not reported. Consequently, the underreporting prevents stakeholders from making informed decisions about necessary funding to improve control strategies.

Accordingly, Keita et al. (2020) reported that only 19% of dogs in Bamako, capital of Mali, had a valid certificate for a rabies vaccination; in two mass vaccination campaigns in 2015 and 2017, the coverage only reached 25% in certain communities (Mauti et al., 2017). Nonetheless, mass vaccination of dogs is the best option both financially and operationally as a means to eliminate rabies in humans (Mindekem et al., 2017). Mindekem et al. focused mainly on premature deaths of rabies victims, estimated using bite records from two regions and extrapolating conclusions for the entirety of Mali. They calculated the burden of rabies using the criterion number of years of life lost (YLL). Additionally, they assessed financial cost based on lost productivity through YLL and health care costs. They found a higher rabies incidence rate in urban than rural areas, with the highest in the capital city. The companion paper by Traore et al. (2020) analyzed rabies surveillance in Mali from 1999 to 2017, utilizing the data of Keita et al (2020) in order to outline the current situation in the country.

4. Diagnostics

Diagnosis of rabies is not possible based solely on clinical symptoms, therefore suspected cases need to be confirmed by laboratory methods. The direct fluorescent antibody test (DFA) is the gold standard for antigen detection in the brain (Mauti, 2019). However, an expensive fluorescence microscope and incubator are needed which limits its application to mostly urban centers. Often it is not known how many dogs are killed after bite incidents and how many are actually sent for post mortem diagnosis. Even when a test is done, the results are often not traceable or further communicated to the public health authorities.

A promising option is the direct rapid immune-histochemical test, which requires only a basic light microscope (Durr et al., 2008), because it uses a peroxidase-linked antibody instead of a (fluorescence) fluorescent antibody conjugate. (Lechenne et al. (2016) provide hope for the future with information about the development of field-ready and easy-to-use rapid immunodiagnostic tests (RIDT), based on the lateral flow principle. These are a quick and low maintenance option, which could be a useful solution for remote areas with no access to microscopes. However, there is criticism that they lack accuracy (Eggerbauer et al., 2016), and consequently further improvement is needed.

Importantly, Mbilo et al. (2020) pointed out in their review that even

if there are reliable methods available to diagnose rabies, obtaining permission from family members after a suspected rabies victim's death to take brain tissue samples can be difficult (Dacheux et al., 2008). Other problems to be monitored are the poor level of experience in rabies laboratory diagnosis, high staff turnover and the need for practical training courses. Rapid diagnostic tests are particularly useful in remote places with no access to microscopes, and these tests can then later be confirmed at the central laboratory (Lechenne et al., 2016). Rapid tests could also be used to test suspected cats, cows, sheep, donkeys and other livestock, although their role in transmission is less important.

The paper "Challenges to improved animal rabies surveillance: Experiences from pilot implementation of decentralized diagnostic units in Chad" by (Naissengar et al., 2021), extended rabies surveillance, previously only available in N'Djamena, to selected provincial rural and urban areas. Nine decentralized diagnostic units (DDU) were established, hosted by veterinary district agencies (VDA) in four different administrative regions. Eighty nine percent of all 178 samples reported to the central veterinary laboratory during the project period tested positive. The possibility for local testing through RIDT was very welcomed by local veterinary staff and preliminary insights suggest a positive influence on One Health communication and PEP initiation. Major shortcoming of the approach was the high cost per sample and limited sustainability beyond the project timeframe.

Voupawoe (Voupawoe et al., 2021) "*Rabies control in Liberia: Joint efforts towards Zero by 30*") report on the establishment of animal rabies diagnostics, fostering collaboration between all rabies control stakeholders, and developing a short-term action plan for rabies control and elimination in Liberia. Better surveillance is desperately needed to guide rabies prevention and control to achieve the goal of zero dog-mediated human rabies by 2030, as defined by the World Health Organization and partners in 2015.

A molecular epidemiological study on the "Use of partial N-gene sequences as a tool to monitor progress on rabies control and elimination efforts in Ethiopia" by (Binkley et al., 2021) points out towards a long-standing dog rabies epizootic in central Ethiopia with potential divergence of a wildlife rabies cycle in side-striped jackals.

For their article "*Molecular study of rabies virus in slaughtered dogs in Billiri and Kaltungo local government areas of Gombe state, Nigeria*", Suleiman et al. (2020) sampled 50 dogs slaughtered for consumption in Gombe State. The sequence phylogenetic analysis uncovered a cluster relationship with rabies viruses from Nigeria, Cameroon, Chad and Niger, characterizing them together as Africa 2 lineage. This genetic relationship could originate through cross-border dog trade movement or seasonal transhumance. Genetic analysis can help to improve surveillance of dog movements and rabies transmission routes in Africa.

5. Control and Prevention

In "*Short communication on the use of a free rabies hotline service in Chad*", (Mbaipago et al., 2020a) considered data collected from 2016 to 2018 through a mobile phone service (hotline) providing professional guidance following animal bites in the population. Mobile phone ownership soared recently in low and middle income countries (LMICs), so this new method is a unique opportunity to reach rural communities and mobile pastoralists, who are very numerous in a largely Sahelian country like Chad. It is also a chance to connect human and animal health services under the One Health approach in areas where their communication is not established due to lack of means.

The hotline received calls about possible human exposures, coming mostly from the public, and gathered information on the status of individual animals, mainly dogs, suspected of rabies. The hotline team advised callers regarding appropriate measures to take, like requesting PEP at the closest health facility or contacting veterinary services. They also helped to connect the two departments and advised on treatment.

The study of Mbaipago et al. (2020b) demonstrated that knowledge of health workers was insufficient regarding adequate procedures in suspected cases, which indicated that the free rabies hotline was a very helpful and low-cost intervention for health staff and patients. It achieved exposure and transmission prevention and helped save lives by providing victims with timely, adequate information and medication.

Tetchi et al. (2020a) reported on the Thai Red Cross protocol experience in Côte d'Ivoire. The main objective was to test the feasibility of free rabies PEP based on the Thai Red Cross (TRC) protocol using the intradermal route. This experience was successful through better PEP compliance, ensuring people are prevented from contracting rabies.

Gerber et al. (2020) in "*Rabies Immunoglobulin: Brief history and recent experiences in Côte d'Ivoire*" analyze the real impact of rabies immunoglobulin in combination with the latest vaccines. The impact of rabies immunoglobulins in the West- and Central African context has never been examined before. The results show that the application of equine rabies immunoglobulin (eRIG) did not lead to a significant reduction of rabies burden in the study population. However, the authors point out that a possible benefit of eRIG administration in severe cases cannot be ruled out based on their findings.

In "Preparing Liberia for Rabies control: Understanding human-dog relationship and practices in Liberia". (Voupawoe et al., 2021)used dog-human ratios in rural and urban districts of Liberia to estimate the cost of a national Liberian dog mass vaccination campaign. Such estimations are important for the planning of mass vaccination campaigns and corresponding financing instruments like development impact bonds (Anyiam et al., 2017).

As a perspective towards integrated disease control, "*Evaluation of integrated control of three dog transmitted zoonoses: rabies, visceral leishmaniasis and cystic echinococcosis, in Morocco", by (El Berbri et al., 2020)* reported on the implementation of a simultaneous disease control scheme against three dog transmitted zoonoses, rabies, visceral leishmaniasis, and cystic echinococcosis in Morocco. Such approaches are highly cost-effective in situations where multiple diseases affect multiple species of domestic animals.

Since there is no cure for rabies after the onset of clinical symptoms, patient death is almost always certain, meaning prevention and post-exposure prophylaxis play a crucial role in the fight against this disease. Gavi decided to include rabies and cholera in its Vaccine Investment Strategy, approved in 2018 (VIS 2018). Gavi called for projects to estimate the overall cost of providing post-exposure prophylaxis to all Gavi-eligible countries. As mentioned above, this *Special Issue* elaborates on the Gavi funded work in Chad, Mali and Côte d'Ivoire. Our estimates indicate that rabies is endemic in West and Central Africa with 1-8 rabies-exposed persons per thousand per year. The estimates of the rabies burden were further used to estimate the potential effect of improved provision of rabies PEP in Gavi-eligible countries by the WHO rabies modelling consortium. The results show that improved PEP, using the newly recommended intradermal regime, can prevent almost half a million deaths between 2020 and 2035, but will still not lead to elimination of rabies (WHO Rabies Modelling Consortium, 2019). The authors clearly pointed out that only dog mass vaccination can lead to elimination of rabies. However, vaccinating dogs is not part of the Gavi VIS, which focuses only on human PEP. Furthermore, Gavi paused all VIS 2018 activities because of the Covid-19 pandemic until further notice. This affects a new project on the use of blockchain secured electronic patient recording to increase human PEP completion rate in Mali and Côte d'Ivoire, funded by the European Developing Countries Clinical Trial Partnership (EDCTP), in its attempt to promote these countries as early adopters of the Gavi VIS 2018.

Rabies control is coordinated by the Pan-African Network for Rabies Control which is part of the Global Alliance for Rabies Control (Mauti, 2019). They emphasize that the One Health approach must be reinforced, as to date the collaboration between human and animal medicine is generally weak or nonexistent in LMICs. In 2016, the online African rabies epidemiological bulletin (https://rabiesalliance.org/networks/paracon/bulletin) was launched, reporting on case numbers, vaccination coverage, dog populations and more. It supports

governments to make fact-based decisions to implement national control strategies.

Paradoxically, although dog mass vaccination can eliminate rabies (Zinsstag et al., 2017) and the cumulative cost of dog mass vaccination with PEP is clearly lower than the cumulative cost of PEP alone after ten years, there is not yet a similar global engagement for well-coordinated dog mass vaccination campaigns to eliminate rabies in Africa. Despite the laudable efforts of Pan-African Rabies Control Network

(PARACON) (Scott et al., 2015), dog rabies control in Africa remains currently fragmented. The very limited efforts by national governments are not to the scale and intensity required for effective elimination. In the review of 22 West and Central African countries, only two countries had reached Level 2 on the Stepwise Approach towards Rabies Elimination (SARE) ladder, the position that reflects a national government has truly prioritized rabies elimination. Overall, dog rabies elimination remains stuck due to lack of government commitment and financial constraints (Mbilo et al., 2020).

6. The way forward

For successful rabies elimination, not only are intensified national efforts necessary but also a strong regional continental coordination to prevent countries freed from rabies being re-infected from neighboring countries. This can be documented from the experiences of elimination of fox rabies in Europe (Freuling et al., 2013) and the almost completed rabies elimination in Latin America, coordinated by the Pan American Health Organization (Belotto, 2004). The most forward looking plan for dog rabies elimination in Africa is depicted in Fig. 1 and demonstrates the important need for regional coordination between involved countries to avoid cross-border transmission and return of the disease into rabies-free zones. A preliminary estimate of the cost of dog rabies elimination in West- and Central Africa is in the range of 1 billion USD (Mauti, 2019). As the estimation for Côte d'Ivoire shows (Kallo 2021), This cost is clearly lower than the cumulated annual financial societal losses from rabies and can be borne by the West- and Central African countries. National governments and regional cooperation networks like the Economic Community of West African States (ECOWAS) and the African Union – Interafrican bureau for animal resources (AU-IBAR) are the most legitimate drivers for the coordination of dog rabies elimination in West – and Central Africa.

Given the accumulated knowledge on dog rabies epidemiology and control to which this *Special Issue* further contributes, a vision of a rabies-free Africa is a realistic scenario and could be achieved in the time span of 20-30 years. Based on existing economic analyses and financial estimates, an amount of 2-3 billion Euro would be sufficient. The estimated amount of money is either spent mostly by patients and dog owners on PEP in the same time period without any effect on on-going transmission, or it can be invested on dog mass vaccination and PEP with the prospect of lasting elimination. The decision, which way to follow is essentially in the hands of African governments.

To inform national governments and regional organizations, from the research presented in this *Special Issue* and the current state of knowledge, we propose a vision "Towards dog rabies elimination in West and Central Africa as a policy brief" (2020), presented as an annex to this paper. The policy brief is translated into French and Portuguese, available to all governments in West and Central Africa for a regionally concerted coordinated approach towards rabies control and elimination Fig. 3.

Fig. 3. Scenario of a possible cross-border spatio-temporal dynamic of dog rabies elimination in the context of a Pan-African campaign (Mauti, 2019).

Declaration of Competing Interest

The authors declare no conflict of interest

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Cora Helle[a,b], Monique Lechenne[a,b], Abdallah Traoré[c], Bassirou Bonfoh[a,b,d], Lisa Crump[a,b], Norbert W. Brattig[e], Jakob Zinsstag[a,b,*]

[a] *Swiss Tropical and Public Health Institute, PO Box, 4002 Basel, Switzerland*

[b] *University of Basel, Petersplatz 1, 4003 Basel, Switzerland*

[c] *Laboratoire Central Vétérinaire, PO Box 2295, Bamako, Mali*

[d] *Centre Suisse de Recherche Scientifique en Côte d'Ivoire (CSRS), Abidjan, Côte d'Ivoire*

[e] *Bernhard Nocht Institute for Tropical Medicine, Hamburg, Germany*

[*] Correspondence author:
E-mail address: jakob.zinsstag@swisstph.ch (J. Zinsstag).