

ORIGINAL ARTICLE - PUBLIC HEALTH

SECONDARY DATA ANALYSIS OF RABIES DEATHS REPORTED IN TAMIL NADU FOR THE LAST 5 YEARS (2018-2022) FROM THE CASE INVESTIGATION FORMS (CIF).

Anandan Mohan ⁽¹⁾, Sankarmani Ramasamy Mathivanan ⁽¹⁾, Palani Sampath ⁽¹⁾,
Avudaiselvi Rathinasamy ⁽¹⁾, Sudhakar Thangarasu ⁽¹⁾, Selvavinayagam T S ⁽¹⁾

(1) Directorate of Public Health and Preventive Medicine, Chennai.

Abstract

BACKGROUND : Rabies is a neglected zoonotic disease that is highly prevalent in low and middle-income countries. It is caused by the bite of rabies-infected animals and is fatal if not treated timely with post-exposure prophylaxis. In spite of several initiatives by the government, India is still the leading country for rabies death globally. It is high time the gaps in the program are assessed and rectified.

METHODOLOGY : We conducted this retrospective descriptive study using the secondary data from the case investigation form (CIF) obtained following a rabies death and analyzed the factors. A total of 121 CIF from rabies death that occurred from 2018 to 2022 were collected and analysed.

RESULTS : Majority of victims were males between the age of 41 to 50 years and less than 1% of them were completely vaccinated. Pet dogs were the major source of infection and lower limb was predominantly involved in the animal bites. Government institutions were the preferred site for wound care and treatment while the private institution was preferred for the management of rabies-infected victims. The incubation period varied from less than a month to one year.

CONCLUSION : It was evident from the study that rabies death was due to lack of awareness about the treatment among the rabies victims leading to poor compliance. There is a need for frequent training in animal bite care and management and reporting among the healthcare workers to reduce the rabies death. It is high time initiatives are taken to achieve zero death due to rabies by 2030.

KEYWORDS : Rabies, Animal bite, Management, Immunoglobulin, vaccine.

INTRODUCTION

Rabies is a vaccine-preventable zoonotic disease caused by the rabies virus of the rhabdovirus family, genus *Lyssaviruses* which affects the central nervous system. It is prevalent in around 150 countries and territories.^{1,2} However, there is currently no treatment and is fatal once the symptoms appear with 100% mortality while the transmission of rabies can be prevented with proper wound care and post-exposure prophylaxis with vaccines with or without immunoglobulin.³ It is transmitted through bites or scratches of rabies-infected domestic or wild animals of which dogs contribute to 99% of rabies mortality. Rabies leads to tens of thousands of deaths every year with 95% of deaths occurring in Asia and Africa and 40% of the victims are school-going children.^{1,4} The exact number of deaths due to rabies is probably underestimated because of poor surveillance, reporting, and a lack of laboratory testing capacity.^{1,5}

To prevent the rabies death and to achieve the goal of zero death due to rabies, post-exposure prophylaxis (PEP) should be started and completed when there is an exposure to an animal that is either suspected or confirmed to be infected by rabies or when there is uncertainty regarding the circumstances that led to the exposure.^{6,7} The PEP includes a thorough wound wash with soap and water and appropriate

wound care, application of a virucidal agent to reduce the viral inoculum, a full course of post-exposure anti-rabies vaccination on day 0,3,7 and 28 to induce antibodies that reduce the risk of the virus entering the peripheral nerves, and a prompt diagnosis and treatment of the animal exposure.^{8,9} Category III, which is defined as single or multiple transdermal bites, scratches or licks on broken skin, and contamination of mucous membrane with animal saliva^{4,6,10} has to be managed with Rabies Immunoglobulins (RIG) which is either a Human RIG or Equine RIG in addition to the PEP.¹¹

Rabies has been eliminated in several high-income countries and controlled in some middle-income countries while rabies due to dog bite has been endemic in most of Asian and African countries. Some of the Asian countries like Thailand, Philippines and Sri Lanka have reduced the mortality and burden due to rabies while it remains high in India and its neighbouring countries like Bangladesh and Pakistan. The burden affects the poor and rural communities



Please Scan this QR Code to

View this Article Online

Article ID: 2023:03:04:04

Corresponding Author : Anandan Mohan

email : mohandoc2k@gmail.com

while children are most likely to be sufferers.⁵ Long before Aristotle recognised the illness in the Greco-Roman era, rabies had been recognised in India for many millennia. The ancient Vedic literature "Sushruta Samhita" offers grave depictions of rabies in both animals and humans.¹³ Rabies is endemic in India and is prevalent in all states and union territories of India except Andaman & Nicobar Islands, Lakshadweep Islands and Goa.⁶

With little intersectoral coordination, rabies is typically only controlled in a few urban areas. Through improved coordination and communication between the animal- and human-health sectors as well as other pertinent industries, India has now established a One Health network that will not only address rabies but also strengthen surveillance and health systems for numerous health risks at the human-animal-environment interface. With this context, in India, 'National Action Plan for Dog Mediated Rabies Elimination' (NAPRE) programme has been launched with the aim of reducing human deaths, caused due to dog-mediated rabies, to zero by 2030.⁷

In India, Tamil Nadu is the first state to launch a multisectoral, statewide rabies control strategy. To find patterns at the district level in the state, surveillance data on dog bites were triangulated with data on vaccination rates and dog populations. Different departments in Tamil Nadu that shared similar goals carried out rabies control initiatives.¹⁴ Other targeted treatments, including proper waste management, animal birth control, anti-rabies vaccination, awareness campaigns, and widespread availability of anti-rabies vaccine at all public health facilities, were also implemented in addition to animal census, and public health surveillance.¹⁰ There are a few retrospective studies to determine the factors leading to mortality due to rabies in animal bite cases globally and studies in Tamil Nadu are limited to selective districts or clusters. With this knowledge this study was conducted in the entire state of Tamil Nadu to assess the determinants for contracting rabies due to animal bites leading to mortality between the years 2018 to 2022.

MATERIALS AND METHODS

STUDY DESIGN AND POPULATION: This retrospective descriptive cross-sectional study was conducted in Tamil Nadu during the months of June to August 2023 to assess the determinants of mortality in rabies related deaths from the Case Investigation Form (CIF) collected following death of a rabies victim. This study included all cases of deaths due to rabies between 2018 to 2022. It was collected from the records of Zoonotic division of the Communicable Disease section of

The Directorate of Public Health and Preventive Medicine (DPH & PM) where the death due to rabies are recorded. The number and cases of deaths due to rabies obtained from Zoonotic division of the Communicable Disease section of DPH & PM were cross verified with the CIF collected from the district. The secondary data of the rabies victims regarding the determinants leading to death were obtained from the standard CIF used in Tamil Nadu for reporting after obtaining permission from the Director of Public Health and Preventive Medicine.

STUDY TOOL: CIF is a verbal autopsy tool which is a standard form used in Tamil Nadu to interview and collect details from the relatives or close acquaintances of the deceased to ascertain the cause of death in circumstances where the cause of death is lacking, or adequate information's are unavailable. It is semi structured questionnaire administered by a trained health care workers (Medical Officers) which consists of details regarding the victims (i) socio-demographic particulars, (ii) details regarding illness mentioning the date of onset of symptoms, place of care, and details on requirements of hospitalisation or not, (iii) clinical features and symptoms, (iv) history of exposure including date of attack, nature and extent of injury, site of injury, (v) source of infection and status of the source, (vi) treatment and post exposure prophylaxis, (vii) control measures by the health department and (viii) conclusion remarks.

DATA EXTRACTION: CIF of all the victims during the study period were collected, verified, and scanned. All the collected CIF forms were manually entered in the Microsoft Excel and cross verified by peers to exclude any errors while entering and coding. The data was analysed using OpenEpi a free web based statistical tool. The results are described in diagrammatic representation, tabular representation, and narrative summaries.

ETHICAL CONSIDERATION: Any mortality due to rabies is considered as a public health importance and appropriate response measures are to be initiated to prevent an outbreak. Permission to conduct this study was obtained from The Director of Public Health and Preventive Medicine, Tamil Nadu. To protect the confidentiality, the victims' and the informant's names were not mentioned in the data collected. In addition, the ethics committee were assured that the names of the victims and the informants would be kept secret.

RESULTS

A total of 37,71,496 cases of dog bites, and 121 rabies related deaths were registered in the Zoonotic division of the Communicable Disease section between the years 2018

to 2022 and CIF was available from all the 121 deaths due to rabies. The mean age of the victims was 49.9±19.1 years ranging from one to 83 years of age. Almost 25% (n=30)

Table 1 : Socio-demographic characteristics of the rabies victims

Factors	Frequency	Percent	95% CI
Sex			
Female	24	19.8	13.1 to 28.1
Male	97	80.2	91.9 to 86.9
Age			
< 10 years	12	9.9	5.2 to 16.7
11 - 20 years	10	8.3	4.0 to 14.7
21 - 30 years	16	13.2	7.8 to 20.6
31 - 40 years	17	14	8.4 to 21.5
41 - 50 years	30	24.8	17.4 to 33.5
51 - 60 years	21	17.4	11.1 to 25.3
61 - 70 years	11	9.1	4.63 to 15.7
> 70 years	4	3.3	0.9 to 8.25
Education			
Graduate	9	7.4	3.5 to 13.7
Higher Secondary school	5	4.1	1.4 to 9.4
High school	13	10.7	5.9 to 17.7
Middle school	30	24.8	17.4 to 33.5
Primary school	23	19	12.5 to 27.1
Illiterate	41	33.9	25.5 to 43.1
Occupation			
Professional	1	0.8	0.2 to 4.5
Student	21	17.4	11.1 to 25.3
Skilled	4	3.3	0.9 to 8.3
Semiskilled	32	26.4	18.8 to 35.2
Unskilled	63	52.1	42.8 to 61.2
Religion			
Hindu	110	90.9	84.3 to 95.4
Christian	8	6.6	2.9 to 12.6
Muslim	3	2.5	0.5 to 7.1
Local body			
Corporation	10	8.3	4.0 to 14.7
Municipality	13	10.7	5.9 to 17.7
Town Panchayat	13	10.7	5.9 to 17.7
Village Panchayat	85	70.2	61.3 to 78.2

Table 2 : History of exposure to the biting animal and the type of injury.

Factors	Frequency	Percent	95% CI
Biting Animal			
Dog	101	83.5	75.6 to 89.6
Cat	4	3.3	0.9 to 8.3
Not known	16	13.2	7.8 to 20.6
Immunisation status of the biting animal			
Fully	3	2.5	0.5 to 7.1
Partially	4	3.3	0.9 to 8.25
Not immunised	58	47.9	38.8 to 57.2
Not known	56	46.3	37.2 to 66.6
Status of biting animal			
Stray animal	41	33.9	25.6 to 43.1
Household pet	39	32.2	24.0 to 41.3
Neighbours pet	12	9.9	5.2 to 16.7
Not Known	29	24.0	
Suspicion of rabies among the biting animal			
Yes	26	21.5	14.5 to 29.9
No	15	12.4	7.1 to 19.6
Not known	80	66.1	56.95 to 74.5
Place of attack			
Home	48	39.7	30.9 to 49.0
Street	47	38.8	30.1 to 48.1
Forest	1	0.8	0.2 to 4.5
Others	7	5.8	2.3 to 11.6
Not Known	18	14.9	9.1 to 22.5
Nature of Exposure			
Bite	94	77.7	69.2 to 84.8
Lick	2	1.7	0.2 to 5.8
Scratch	13	10.7	5.9 to 17.7
Not Known	12	9.9	5.2 to 16.7
Extent of Injury			
Single	66	54.5	45.2 to 63.6
Multiple	25	20.7	13.8 to 28.9
Not Known	26	21.5	14.5 to 29.9
No injury	4	3.3	0.9 to 8.25
Site of Injury			
Lower limbs / toes	46	38.0	29.4 to 47.3
Upper limbs / fingers	37	30.6	22.5 to 39.6
Head/face / neck	17	14.0	8.4 to 21.5
Genitalia	1	0.8	0.2 to 4.5
Not Known	20	16.5	10.4 to 24.4
Category of bite			
II	15	12.4	7.1 to 19.6
III	89	73.6	64.8 to 81.2
Not known	17	14.0	8.4 to 21.5

Table 3 : Treatment and Post exposure prophylaxis.

Factors	Frequency	Percent	95% CI
Observation of the biting animal for 14 days			
Yes	18	14.9	9.1 to 22.5
No	52	43	34.0 to 52.3
Not known	51	42.1	33.2 to 51.5
Local wound treatment			
Yes	25	20.7	13.8 to 28.9
No	96	79.3	71.0 to 86.2
Inj. Tetanus toxoid administration			
Yes	34	28.1	20.3 to 37.0
Not given	39	32.3	24.0 to 41.3
Not known	48	39.6	30.9 to 49.0
Anti-Rabies vaccine administration			
Completed	1	0.8	0.2 to 4.5
Not completed	20	16.6	10.4 to 24.4
Not given	55	45.4	36.4 to 54.8
Not known	45	37.2	28.6 to 46.4
Equine rabies immunoglobulin administration			
Completed	4	3.3	0.9 to 8.25
Not given	54	44.6	35.6 to 54.0
Not known	63	52.1	42.8 to 61.2
Human rabies immunoglobulin administration			
Completed	2	1.7	0.2 to 5.8
Not given	59	48.7	39.6 to 58.0
Not known	60	49.6	40.4 to 58.8
Place of diagnosis of rabies			
Government Medical College Hospital	33	27.3	19.6 to 36.2
Government Hospital	22	18.2	11.8 to 26.2
Healers	1	0.8	0.2 to 4.5
Primary Health Centre	10	8.3	4.0 to 14.7
Private Clinic/ Hospital	55	45.5	36.4 to 54.8

Table 4 : History of exposure to the biting animal and the type of injury.

Factors	Frequency	Percent	95% CI
Difficulty in swallowing	81	66.9	57.8 to 75.2
Difficulty in breathing	62	51.2	41.2 to 59.6
Behavioural changes	56	46.3	37.17 to 55.6
Fever	49	40.5	31.7 to 49.8
Aerophobia	48	39.7	30.9 to 49.0
Hyperactivity	47	38.8	30.1 to 48.1
Encephalitis	23	19	12.5 to 27.1
Paralysis	10	8.3	4.0 to 14.7

The mean age of the of the victims were between the age group of 41 to 50 years. Among the death due to rabies 80.2% (n=97) of them were male and 20.7% (n=25) of them were between the age of 41 to 50 years. Majority, 70.2% (n=85) of the victims' residence were from village panchayat/ rural local bodies while only 8.5% (n=10) of the victims were from corporation/ urban local bodies. Almost one third, 35.5% (n=43) of them had middle school education, while 33.9% (n=41) had not attended schooling and 19% (n=23) had primary level of education. Regarding occupation, 52.1% (n=63) were unskilled workers and 26.4% (n=32) were semiskilled workers. First degree relatives were the most common source of information 75.2% (n=91) of the victims. Majority of individuals were attacked either at home 39.7% (n=48) or in the streets 38.8% (n=47). Dogs bites were the major cause of rabies death with 83.5% (n=101) and Category III bites were the most common category of injury with 73.6% (n=89). Regarding injury, 54.5% (n=66) of the victims sustained single injury and 38.8% (n=47) sustained superficial injury with bleeding while 21.5% (n=26) were not aware about the victim's injury. The most common site of injury was lower limbs or toes with 38% (n=46) followed by upper limbs or tips of fingers with 30.6% (n=37).

their height.

When considering the exposure status, bite from animals was the most common presenting history and it was a single exposure with superficial injury leading to bleeding. Similar findings were also presented in other studies on rabies death.^{20,22} Category III animal bite was the most commonly observed finding in our study and other studies in conducted in India, Pakistan, Afghanistan, Philippines, China, and African countries.^{2,4,16} It indicates that there is an increased chance of rabies incidence due to increased possibility of transmission of virus because of the broken skin barrier.

Similar to our study, other studies also presented the fact that the biting animal was not suspected to transmit the disease as in most cases it was a pet and hence, they were not observed adequately for signs and symptoms of rabies in the animals.^{14,16} This could also bring light to the fact that the compliance was poor in wound care and reduced adherence to the treatment as most of the victims did not take PEP and even those who were initiated in PEP were not completely vaccinated.^{4,19,23} These findings necessitates more information, awareness and education towards wound handling and PEP is required for the population to bring down the mortality due to rabies.

Government hospitals were mostly preferred for first aid and medical care by majority of the victims when compared to primary health centres, medical college hospitals and private clinics/ hospitals. Other studies did not provide much light on the place of care following animal bite.¹⁸ This higher preference for government hospitals could be due to an assumption of availability of ARV and ERIG/ HRIG in those centres 24/7. The knowledge on the functioning, availability of ARV and ERIG/ HRIG in other government health facility is still poor among the population. Private hospitals or clinics were most preferred for initial treatment following signs and symptoms of rabies, but they were later referred to Government medical colleges for management due to availability of isolation wards in tertiary care centres. There was failure in ARV and ERIG/ HRIG in few patients in other studies and this finding could not be appreciated in our study as only one of the patient was fully immunised. Even after three dose some succumbed to death due to rabies, this could be the fact that the virus inoculation directly occurred in the peripheral nerve roots.^{11,24,25}

The incubation period observed in our study was identical to other studies and there was no long incubation period lasting more than a year in the victims.^{15,21,26,27} Majority of the victims in our study presented with difficulty in swallowing and hydrophobia followed by difficulty in

breathing. These findings were consistent with most other studies from Asia and Africa^{4,13,15} except for the study in Philippines where altered behaviour and irritability was the frequent observation.¹⁹ This difference could be due to the difference in observation from the first responders following the signs and symptoms or could be due to recall bias which needs further investigation. The duration between the onset of signs and symptoms to death was similar to our study when compared to other studies.

CONCLUSION

Majority of death due to rabies is contributed by dogs and pet dog bites were the major source of infection in rabies deaths compared to stray dog bites. Majority of the victims were males in middle age group who are the productive population. More than half of the rabies deaths occurred in those who did not take vaccines which shows poor adherence to treatment and most of those who took vaccines received it in government institutions which should be improved to reach a hundred percentage coverage. Even in those who took vaccines only few of the victims sought proper PEP for the dog bite and the PEP was not administered or not completed in majority of the victims. Unfortunately, a large proportion of them were not given ARV at first visit which could be due to lack of knowledge among the HCWs in the first place of contact between the animal bite victims and healthcare system. When analysed the Cat III bites, the data on Immunoglobulin administration was inadequate among the victims and only one tenth of them were administered Immunoglobulin which should be improved. The majority of the CIF were incomplete, and in many instances, even simple data is wrongly entered or missed.

RECOMMENDATIONS

It is evident from the aforementioned findings that in addition to stray animals, pet dogs play a major role in disease causation and must receive more attention, and effective monitoring of their immunisation is crucial. Some recommendation to improve male and middle age group vaccination to be given here or that point may be removed from the conclusion if it is not necessary. To improve the compliance in the victims the general population should be educated through information, education, communication (IEC) and behaviour change communication (BCC) using multimedia, visual, and auditory communication means. To identify the gaps in the treatment and care of animal bite victims, it is necessary to verify that HCWs have received training on how to complete a CIF for a rabies death and the

significance of all the facts provided.

FINANCIAL SUPPORT AND SPONSORSHIP

Nil.

CONFLICTS OF INTEREST

There are no conflicts of interest.

REFERENCES

1. Rabies. <https://www.who.int/news-room/fact-sheets/detail/rabies>.
2. Haselbeck, A. H. et al. Challenges to the Fight against Rabies-The Landscape of Policy and Prevention Strategies in Africa. *Int. J. Environ. Res. Public Health* 18, 1–15 (2021).
3. Goel, K. et al. Emergence of rabies among vaccinated humans in India: a public health concern. *Lancet Reg. Heal. - Southeast Asia* 9, (2023).
4. Chikanya, E., Macherera, M. & Maviza, A. An assessment of risk factors for contracting rabies among dog bite cases recorded in Ward 30, Murewa district, Zimbabwe. *PLoS Negl. Trop. Dis.* 15, (2021).
5. Li, A. J. et al. Descriptive assessment of rabies post-exposure prophylaxis procurement, distribution, monitoring, and reporting in four Asian countries: Bangladesh, Bhutan, Cambodia, and Sri Lanka, 2017-2018. *Vaccine* 37 Suppl 1, A14–A19 (2019).
6. National Rabies Control Programme :: National Centre for Disease Control (NCDC). <https://ncdc.mohfw.gov.in/index1.php?lang=1&level=1&sublinkid=146&lid=150>.
7. Adopt One Health, Stop Rabies: India launches new national action plan for dog mediated rabies elimination by 2030. <https://www.who.int/news/item/25-10-2021-adopt-one-health-stop-rabies-india-launches-new-national-action-plan-for-dog-mediated-rabies-elimination-by-2030>.
8. Aziz, H. et al. The current concepts in management of animal (dog, cat, snake, scorpion) and human bite wounds. *J. Trauma Acute Care Surg.* 78, 641–648 (2015).
9. Sahu, D. P., PS, P., Bhatia, V. & Singh, A. K. Anti-Rabies Vaccine Compliance and Knowledge of Community Health Worker Regarding Animal Bite Management in Rural Area of Eastern India. *Cureus* 13, (2021).
10. Abbas, S. S., Venkataramanan, V., Pathak, G. & Kakkar, M. Rabies control initiative in Tamil Nadu, India: a test case for the 'One Health' approach. *Int. Health* 3, 231–239 (2011).
11. Gozdas, H. T. Rabies immunoglobulin should not be forgotten in category III exposure. *Rev. Soc. Bras. Med. Trop.* 54, e04702021 (2021).
12. Changalucha, J., Hampson, K., Jaswant, G., Lankester, F. & Yoder, J. Human rabies: prospects for elimination. *CAB Rev. Perspect. Agric. Vet. Sci. Nutr. Nat. Resour.* 16, (2021).
13. Suraweera, W. et al. Deaths from Symptomatically Identifiable Furious Rabies in India: A Nationally Representative Mortality Survey. *PLoS Negl. Trop. Dis.* 6, e1847 (2012).
14. Kumar, R. & Sinha, S. P. Rapid evaluation of rabies control program: 30-cluster survey in rural area of Perambalur district, Tamilnadu, India. *Int. J. Community Med. Public Heal.* 3, 2627–2632 (2016).
15. Salahuddin, N., Gohar, M. A., Jamali, S., Qureshi, M. A. & Baig-Ansari, N. Analysis of human rabies deaths reported at two hospitals in Karachi, Pakistan: a call to save lives by reforming rabies prevention facilities. *Trans. R. Soc. Trop. Med. Hyg.* 117, 479–484 (2023).
16. Gan, H. et al. Global burden of rabies in 204 countries and territories, from 1990 to 2019: results from the Global Burden of Disease Study 2019. *Int. J. Infect. Dis.* 126, 136–144 (2023).
17. Bharathy, S. & Gunaseelan, L. Study on epidemiological trends of canine rabies between 2011 and 2014 in Chennai city, South India. *Indian J. Anim. Res.* 50, 964–968 (2016).
18. John, D., Royal, A. & Bharti, O. Burden of illness of dog-mediated rabies in India: A systematic review. *Clin. Epidemiol. Glob. Heal.* 12, 100804 (2021).
19. Guzman, F. D. et al. Clinical, epidemiological, and spatial features of human rabies cases in Metro Manila, the Philippines from 2006 to 2015. *PLoS Negl. Trop. Dis.* 16, e0010595 (2022).
20. S, S., A, A., AM, K. & GK, I. Prevalence of Dog Bites

in Rural and Urban Slums of Delhi: A Community-based Study. *Ann. Med. Health Sci. Res.* 6, 115 (2016).

21. Lodha, L., Manoor Ananda, A. & Mani, R. S. Rabies control in high-burden countries: role of universal pre-exposure immunization. *Lancet Reg. Heal. - Southeast Asia* 0, 100258 (2023).

22. Warrell, D. A. The clinical picture of rabies in man. *Trans. R. Soc. Trop. Med. Hyg.* 70, 188–195 (1976).

23. Sudarshan, M. K. et al. Assessing the burden of human rabies in India: results of a national multi-center epidemiological survey. *Int. J. Infect. Dis.* 11, 29–35 (2007).

24. Kumar, S. K., Gupta, P. & Panda, P. K. Death from rabies: The reason being poor compliance to vaccination or it's failure. *J. Fam. Med. Prim. Care* 9, 4437 (2020).

25. Haradhanalli, R. S., Fotedar, N., Kumari, N. & Narayana, D. H. A. Safety and clinical efficacy of human rabies immunoglobulin in post exposure prophylaxis for category III animal exposures. *Hum. Vaccin. Immunother.* 18, (2022).

26. Zhang, J., Jin, Z., Sun, G. Q., Zhou, T. & Ruan, S. Analysis of Rabies in China: Transmission Dynamics and Control. *PLoS One* 6, e20891 (2011).

27. Ramirez-Venegas, A., Torres-Duque, C. A., Guzman-Bouilloud, N. E., Gonzalez-Garcia, M. & Sansores, R. H. SMALLa AIRWAY DISEASE IN COPD ASSOCIATED TO BIOMASS EXPOSURE. *Rev. Invest. Clin.* 71, 70–78 (2019).