Epidemiological Report

Yellow fever

Historic Series 2010 – 2021

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BRIEF HISTORY

Yellow fever (YF) is a disease caused by an arbovirus. In the Americas, the first reports date from the 15th century, while in colonial Brazil outbreaks and epidemics were observed in cities until 1942, when the last case of urban YF occurred in Acre.[1-3] From then on, only sporadic cases of wild YF were observed, mainly in the Amazon region, with periodic expansion to other states, approximately every ten years.

However, the wild form predominated, which, unlike the urban form, which is transmitted by *Aedes aegypti*, is only transmitted by wild mosquitoes, mainly of the *Sabethes* and *Haemagogus* genera. From 1942 to the 1980s, there was no great concern with urbanization, since *A. aegypti* was considered eliminated from the country, that is, there was no such risk. These were only sporadic cases of people who entered the forest without proper vaccination protection. In the 1980s, however, *A. aegypti* was once again found in Brazilian cities and with it, dengue epidemics and the risk of urban YF returned. The expansion of the virus to locations outside the Amazon region became increasingly comprehensive, reaching the Southeast and South. As a result, the areas with yellow fever vaccine recommendations were expanded.

Between 2000 and 2010, there were three outbreaks of YF in the SSP, with 32 human cases and 15 deaths. There was also an expansion of the area with recommendation of immunization against the disease in the state, but not including the South and Southeast regions of São Paulo, the most populous, because the risk of the vaccine against Yellow Fever (visceralization with cases of death) was greater than the risk of spreading the disease in the region at that time. In 2016, the YF virus reached the SSP again, after six years without autochthonous disease. The reintroduction occurred mainly from Minas Gerais (which had already shown an increase in the number of cases in the previous year). The virus continued its expansion to the south and east of São Paulo, reaching regions for which there was no vaccine recommendation and reaching the coast of the state in 2018.

To face the challenge, and without having a vaccine for this entire contingent immediately, an “ecological corridors” model was used, based on the investigation of epizootics (primates killed by YF) to help establish a vaccination schedule in a timely manner. and protect the population that would later be affected. In 2019, most cases occurred in the coastal region of Vale do Ribeira, with some cases also in Vale do Paraíba. As of the third quarter of that year, there were no more autochthonous cases of YF in the SSP. Notifications continue to be monitored, but no autochthonous cases were confirmed in 2020 and 2021.

ETIOLOGICAL AGENT

YF is caused by an arbovirus (viruses transmitted by arthropods that complete their replicative cycle in insects) belonging to the flavivirus genus (a group to which dengue and zika viruses also belong).

TRANSMISSION MODE

YF is not transmitted directly from person to person. In the urban cycle (human-infected-mosquito-human transmission), the virus is transmitted by mosquitoes of the *Aedes* genus (generally *A. aegypti*) and in the sylvatic cycle (transmission between non-human primates or from a non-human primate to humans) by mosquitoes of the *Haemagogus* and *Sabethes* genera. There are reports of transmission by blood products and from mother to fetus.

A patient in the viremic phase of YF who is in a place where there are mosquitoes of the *Aedes* genus needs to stay in an enclosure with screens on the windows to prevent them from being contaminated and transmitting the virus to other people. In addition, a "block" is made in all places where the patient has been to prevent *Aedes* from being contaminated and starting an urban cycle. In forest areas where contamination may have occurred, a vaccination blockade is carried out on people who reside or frequent the region. In urban areas, in addition to the vaccine blockade, a blockade of *Aedes sp* is also carried out, aiming to destroy alates and larvae before they can eventually transmit the disease.

EPIDEMIOLOGICAL SITUATION

Currently, the entire SSP is an area of YF vaccine recommendation. This should guarantee a much broader protection of the population and should allow that blockades through intensifications of vaccination coverage are sufficient to stop the spread and urbanization of the virus. This is what happened in the Northwest of São Paulo in 2016 and 2017: few sparse cases in a region where there was already a vaccine recommendation. Since 2020, no autochthonous human cases have been recorded in the state. That year, there was only one confirmed case, that came from Santa Catarina. All suspected cases reported since then have been discarded.

Surveillance of yellow fever virus expansion has been carried out by monitoring epizootics (death of non-human primates with confirmed YF virus infection). No worrying focus has been identified since 2020 in the territory of São Paulo. Table 1 shows confirmed autochthonous cases of wild YF in the SSP from 2010 to 2021, by probable site of infection (PSI) and onset of symptoms (OS).

Table 1. Confirmed autochthonous cases of wild YF in the SSP, from 2010 to 2021.*

PSI	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	Total
BRAZIL	0	0	0	0	1	1	5	97	481	68	1	0	**654**
AM	0	0	0	0	0	0	0	0	1	0	0	0	**1**
BA	0	0	0	0	0	0	0	0	0	1	0	0	**1**
GO	0	0	0	0	0	1	0	0	0	0	0	0	**1**
MG	0	0	0	0	0	0	2	32	27	0	0	0	**61**
PR	0	0	0	0	0	0	0	0	0	1	0	0	**1**
RJ	0	0	0	0	0	0	0	0	3	0	0	0	**3**
SC	0	0	0	0	0	0	0	0	0	0	1	0	**1**
SP	0	0	0	0	1	0	3	65	450	66	0	0	**585**
ÁGUAS DA PRATA	0	0	0	0	0	0	0	2	0	0	0	0	**2**
AMÉRICO BRASILIENSE	0	0	0	0	0	0	1	2	0	0	0	0	**3**
AMPARO	0	0	0	0	0	0	0	3	0	0	0	0	**3**
APIAÍ	0	0	0	0	0	0	0	0	0	1	0	0	**1**
ARACARIGUAMA	0	0	0	0	0	0	0	0	1	0	0	0	**1**
ARUJÁ	0	0	0	0	1	0	0	0	6	0	0	0	**7**
ATIBAIA	0	0	0	0	0	0	0	8	52	0	0	0	**60**
BADY BASSITT	0	0	0	0	0	0	1	0	0	0	0	0	**1**
BARRA DO TURVO	0	0	0	0	0	0	0	0	0	5	0	0	**5**
BATATAIS	0	0	0	0	0	0	0	1	0	0	0	0	**1**
BIRITIBA-MIRIM	0	0	0	0	0	0	0	0	0	1	0	0	**1**
BOM JESUS DOS PERDOES	0	0	0	0	0	0	0	0	4	0	0	0	**4**
BRAGANÇA PAULISTA	0	0	0	0	0	0	0	1	2	0	0	0	**3**
CAÇAPAVA	0	0	0	0	0	0	0	0	3	0	0	0	**3**
CACHOEIRA PAULISTA	0	0	0	0	0	0	0	0	0	1	0	0	**1**
CAIEIRAS	0	0	0	0	0	0	0	1	3	0	0	0	**4**
CAJATI	0	0	0	0	0	0	0	0	0	4	0	0	**4**
CAMPINAS	0	0	0	0	0	0	0	1	0	0	0	0	**1**
CAMPO LIMPO PAULISTA	0	0	0	0	0	0	0	0	2	0	0	0	**2**
CANANÉIA	0	0	0	0	0	0	0	0	0	4	0	0	**4**
CARAGUATATUBA	0	0	0	0	0	0	0	0	1	1	0	0	**2**
COTIA	0	0	0	0	0	0	0	0	10	0	0	0	**10**
CUNHA	0	0	0	0	0	0	0	0	1	0	0	0	**1**
ELDORADO	0	0	0	0	0	0	0	0	1	15	0	0	**16**

PSI	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	Total
EMBU-GUAÇU	0	0	0	0	0	0	0	0	2	0	0	0	**2**
ESPÍRITO SANTO DO PINHAL	0	0	0	0	0	0	0	0	4	0	0	0	**4**
FRANCISCO MORATO	0	0	0	0	0	0	0	0	2	0	0	0	**2**
FRANCO DA ROCHA	0	0	0	0	0	0	0	1	8	0	0	0	**9**
GUARUJÁ	0	0	0	0	0	0	0	0	1	0	0	0	**1**
GUARULHOS	0	0	0	0	0	0	0	0	23	0	0	0	**23**
IBIÚNA	0	0	0	0	0	0	0	0	12	0	0	0	**12**
IGARATÁ	0	0	0	0	0	0	0	1	3	0	0	0	**4**
IGUAPE	0	0	0	0	0	0	0	0	4	0	0	0	**4**
IPORANGA	0	0	0	0	0	0	0	0	1	19	0	0	**20**
ITANHAEM	0	0	0	0	0	0	0	0	1	0	0	0	**1**
ITAPECERICA DA SERRA	0	0	0	0	0	0	0	0	4	0	0	0	**4**
ITAPIRA	0	0	0	0	0	0	0	0	2	0	0	0	**2**
ITAQUAQUECETUBA	0	0	0	0	0	0	0	0	1	0	0	0	**1**
ITARIRI	0	0	0	0	0	0	0	0	6	0	0	0	**6**
ITATIBA	0	0	0	0	0	0	0	2	1	0	0	0	**3**
JACUPIRANGA	0	0	0	0	0	0	0	0	1	4	0	0	**5**
JARINÚ	0	0	0	0	0	0	0	1	9	0	0	0	**10**
JOANOPOLIS	0	0	0	0	0	0	0	0	1	0	0	0	**1**
JUNDIAÍ	0	0	0	0	0	0	0	1	2	0	0	0	**3**
JUQUIÁ	0	0	0	0	0	0	0	0	1	1	0	0	**2**
JUQUITIBA	0	0	0	0	0	0	0	0	2	0	0	0	**2**
MAIRIPORA	0	0	0	0	0	0	0	32	140	0	0	0	**172**
MIRACATU	0	0	0	0	0	0	0	0	6	0	0	0	**6**
MONTE ALEGRE DO SUL	0	0	0	0	0	0	0	3	2	0	0	0	**5**
MONTEIRO LOBATO	0	0	0	0	0	0	0	0	11	0	0	0	**11**
MORUNGABA	0	0	0	0	0	0	0	0	1	0	0	0	**1**
NATIVIDADE DA SERRA	0	0	0	0	0	0	0	0	1	0	0	0	**1**
NAZARÉ PAULISTA	0	0	0	0	0	0	0	1	28	0	0	0	**29**
PARIQUERA-AÇU	0	0	0	0	0	0	0	0	0	5	0	0	**5**
PEDRO DE TOLEDO	0	0	0	0	0	0	0	0	1	0	0	0	**1**
PERUÍBE	0	0	0	0	0	0	0	0	1	0	0	0	**1**
PIEDADE	0	0	0	0	0	0	0	0	5	0	0	0	**5**

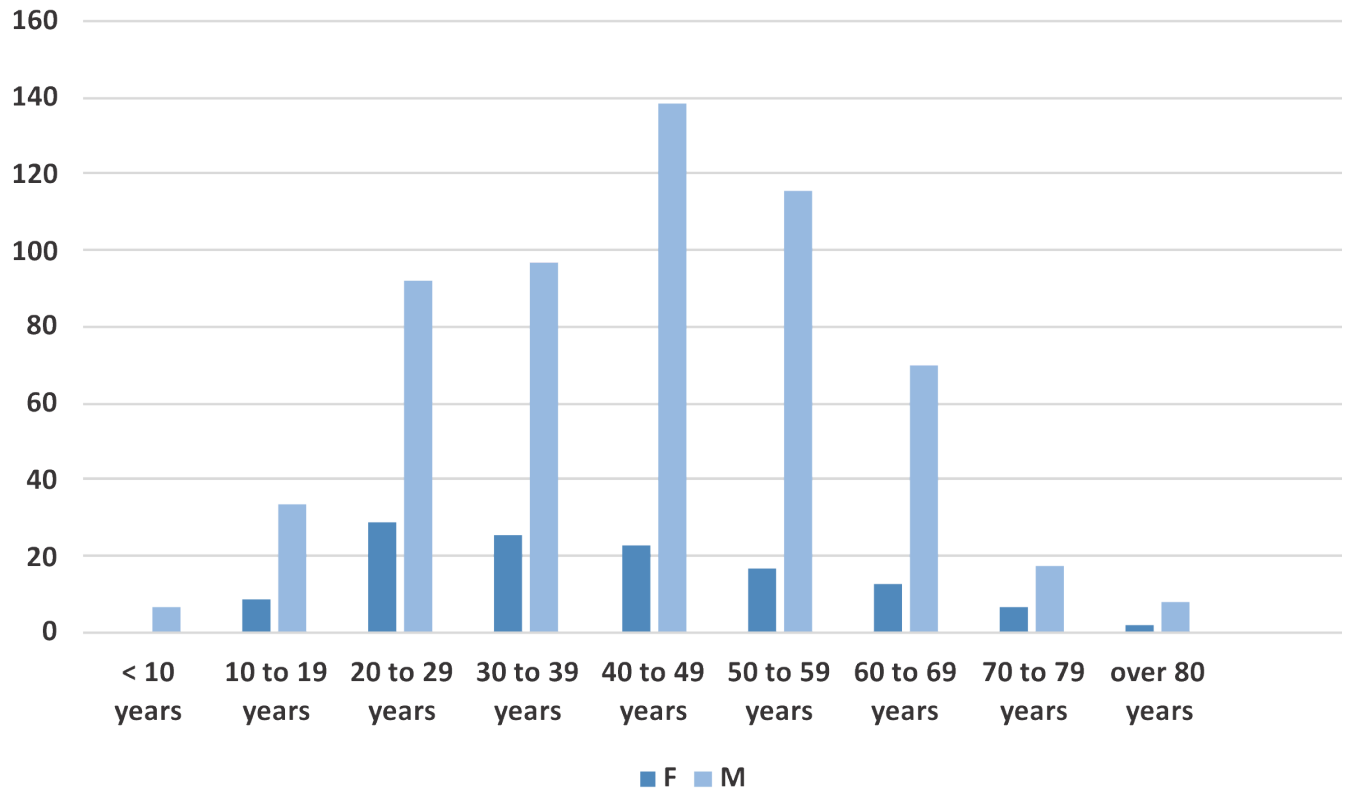
PSI	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	Total
PIRACAIA	0	0	0	0	0	0	0	0	7	0	0	0	**7**
QUELUZ	0	0	0	0	0	0	0	0	1	0	0	0	**1**
REGISTRO	0	0	0	0	0	0	0	0	0	2	0	0	**2**
RIBEIRA	0	0	0	0	0	0	0	0	0	1	0	0	**1**
RIBEIRAO BRANCO	0	0	0	0	0	0	0	0	0	1	0	0	**1**
RIBEIRÃO PRETO	0	0	0	0	0	0	1	0	0	0	0	0	**1**
SALTO DE PIRAPORA	0	0	0	0	0	0	0	0	1	0	0	0	**1**
SANTA CRUZ DO RIO PARDO	0	0	0	0	0	0	0	1	0	0	0	0	**1**
SANTA ISABEL	0	0	0	0	0	0	0	0	12	0	0	0	**12**
SANTA RITA DO PASSA QUATRO	0	0	0	0	0	0	0	0	1	0	0	0	**1**
SÃO BENTO DO SAPUCAÍ	0	0	0	0	0	0	0	0	3	0	0	0	**3**
SÃO JOÃO DA BOA VISTA	0	0	0	0	0	0	0	1	1	0	0	0	**2**
SÃO JOSÉ DOS CAMPOS	0	0	0	0	0	0	0	0	7	0	0	0	**7**
SÃO MIGUEL ARCANJO	0	0	0	0	0	0	0	0	1	0	0	0	**1**
SÃO PAULO	0	0	0	0	0	0	0	1	14	0	0	0	**15**
SÃO ROQUE	0	0	0	0	0	0	0	0	3	0	0	0	**3**
SÃO SEBASTIÃO	0	0	0	0	0	0	0	0	2	0	0	0	**2**
SERRA NEGRA	0	0	0	0	0	0	0	0	0	1	0	0	**1**
SOROCABA	0	0	0	0	0	0	0	0	1	0	0	0	**1**
TAMBAÚ	0	0	0	0	0	0	0	0	2	0	0	0	**2**
TAPIRAÍ	0	0	0	0	0	0	0	0	1	0	0	0	**1**
TAUBATÉ	0	0	0	0	0	0	0	0	3	0	0	0	**3**
TUIUTI	0	0	0	0	0	0	0	1	0	0	0	0	**1**
UBATUBA	0	0	0	0	0	0	0	0	8	0	0	0	**8**
VALINHOS	0	0	0	0	0	0	0	0	9	0	0	0	**9**
IGNORED	0	0	0	0	0	0	0	7	43	3	0	0	**53**
Overall Total	**0**	**0**	**0**	**0**	**1**	**1**	**5**	**104**	**524**	**71**	**1**	**0**	**707**

Source: SINAN-NET/CVE/DVZOO. *Provisional data until May 4, 2022.

During the epidemic, there were 129 confirmed non-autochthonous cases, mainly at the beginning, when many cases were registered in São Paulo territory of people infected in Minas Gerais, a neighboring state where many people had gone to spend the holidays with their families.

Graph 1 shows the distribution of confirmed cases of wild YF in the SSP from 2010 to 2021, by sex and age. Note the characteristic distribution of this form of the disease, with a marked predominance in males of working age. This is even observed in municipalities where there was an "explosion" of cases in a short time, such as Atibaia and Mairiporã, which could lead to the hypothesis of transmission by *Aedes*, also abundant in both places.

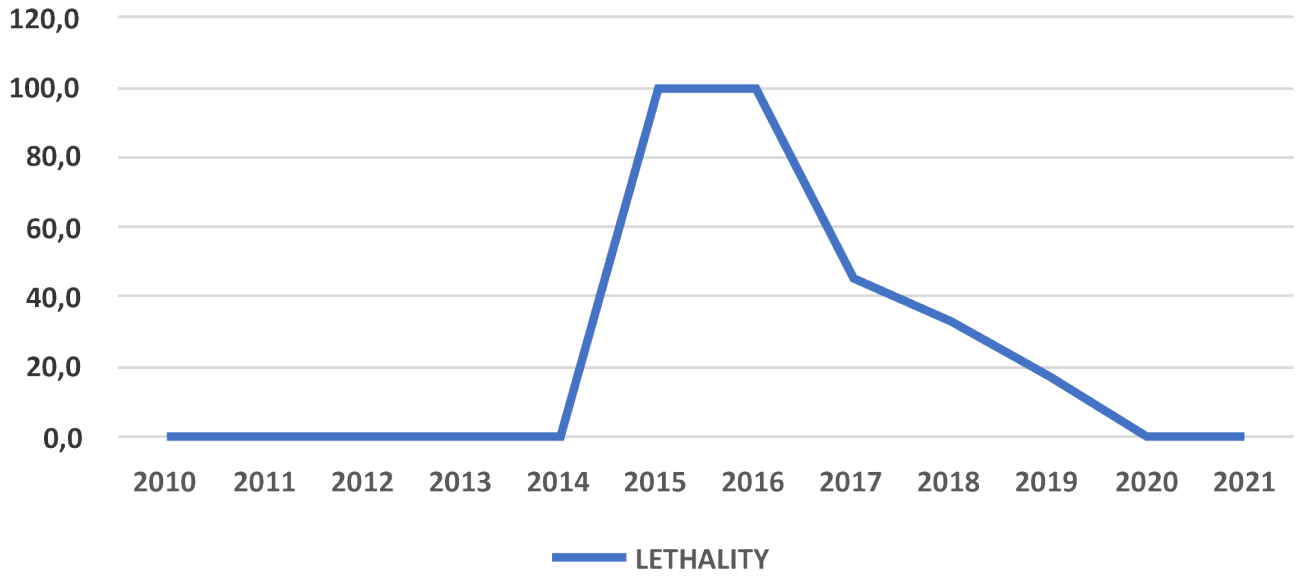
Graph 1. Distribution of confirmed cases of wild YF in the SSP from 2010 to 2021*, by sex and age group.



Source: SINAN-NET/CVE/DVZOO. *Provisional data until May 4, 2022.

Graph 2 shows the number of cases and the lethality of sylvatic YF cases confirmed in the state of São Paulo, from 2010 to 2021. It is noted that the lethality, initially very high, was gradually reduced. This was due not only to the reduction in the number of cases, which allowed for better care and hospitalization in places with more resources, but also due to the greater experience of the services in the management of patients. It should be noted that, contrary to what happens in dengue, there is no way to prevent the worsening of yellow fever cases. The management of patients with severe YF requires admission to hospitals with very advanced resources, such as hemodialysis, plasmapheresis and even liver transplantation.

Graph 2. Number of confirmed cases and case fatality of wild YF cases in the SSP from 2010 to 2021.*



Source: SINAN-NET/CVE/DVZOO. *Provisional data until May 4, 2022.

Table 2 shows the evolution of wild YF cases in the SSP from 2010 to 2021, in relation to YF vaccination administered at different times in relation to the OS of the disease.

Table 2. Distribution of confirmed cases of wild YF in the SSP, from 2014 to 2021*, by vaccination status and evolution.

YF VACCINATION HISTORY	2014	2015	2016	2017	2018	2019	2020	Total
VACCINE AFTER OS	0	0	0	5	21	8	0	**34**
VACCINATED, NOT IMMUNIZED - VACCINATION VIREMIA?	0	0	0	2	59	9	0	**70**
VACCINATED, NOT IMMUNIZED - VIREMIA = DISEASE	0	0	0	0	10	0	0	**10**
POSSIBLE VACCINATION FAILURE	0	0	0	0	20	6	0	**26**
N/A	1	1	5	97	414	48	1	**567**
Overall Total	**1**	**1**	**5**	**104**	**524**	**71**	**1**	**707**

Source: SINAN-NET/CVE/DVZOO. *Provisional data until May 4, 2022.

When the epidemic reached places without previous vaccine recommendation, the immunobiological was applied according to the prediction of when the virus would arrive according to the model of “ecological corridors”. This meant that, in most places, the vaccine arrived shortly before the virus. There were those who were vaccinated shortly before the onset of symptoms (when they were already in the incubation period), on the first day of symptoms and even a little later.

As expected, most cases occurred in unvaccinated individuals or in individuals who, despite having received the vaccine, were not yet protected when bitten by the infected mosquito. In addition, many symptomatic cases that occurred shortly after receiving the vaccine created confusion between the hypotheses of YF and post-vaccination adverse events. Confusion that in some cases was resolved by sequencing the virus, establishing whether the origin was vaccinal or wild. However, if only sequencing was considered in the differentiation, most cases would be without definitive classification. Therefore, the Division of Vector-Transmitted Diseases and Anthropozoonoses, together with the Immunization Division, established epidemiological and clinical criteria to classify these dubious cases, which occurred in large numbers in the ten days following vaccination. For example, if the onset of symptoms was on the day of the vaccine, or earlier, it could not be adverse events following immunization (AEFI); if the patient had received the vaccine, but had not attended any place with the possibility of transmission, it would most likely be an AEFI, and so on.

Adding up those who were not vaccinated (565) and those who did not know if they had been vaccinated (44), those who had received the immunizing agent, but were not yet immunized when they became infected (83), those who were vaccinated on the day the symptoms or after (38) and those who were vaccinated on an unknown date (9), we have that 739 of the 753 patients were not truly immunized when they acquired the disease. This is really to be expected for a vaccine with as high an efficacy as that of YF. In 14 cases, there was a possible vaccine failure, that is, they were vaccinated in a timely manner and still acquired the disease, with three progressing to death.

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