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## Review

## Viral infections in workers in hospital and research laboratory settings: a comparative review of infection modes and respective biosafety aspects

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## SUMMARY

**Objectives:** To compare modes and sources of infection and clinical and biosafety aspects of accidental viral infections in hospital workers and research laboratory staff reported in scientific articles.

**Methods:** PubMed, Google Scholar, ISI Web of Knowledge, Scirus, and Scielo were searched (to December 2008) for reports of accidental viral infections, written in English, Portuguese, Spanish, or German; the authors' personal file of scientific articles and references from the articles retrieved in the initial search were also used. Systematic review was carried out with inclusion criteria of presence of accidental viral infection's cases information, and exclusion criteria of absence of information about the viral etiology, and at least probable mode of infection.

**Results:** One hundred and forty-one scientific articles were obtained, 66 of which were included in the analysis. For arboviruses, 84% of the laboratory infections had aerosol as the source; for alphaviruses alone, aerosol exposure accounted for 94% of accidental infections. Of laboratory arboviral infections, 15.7% were acquired percutaneously, whereas 41.6% of hospital infections were percutaneous. For airborne viruses, 81% of the infections occurred in laboratories, with hantavirus the leading causative agent. Aerosol inhalation was implicated in 96% of lymphocytic choriomeningitis virus infections, 99% of hantavirus infections, and 50% of coxsackievirus infections, but infective droplet inhalation was the leading mode of infection for severe acute respiratory syndrome coronavirus and the mucocutaneous mode of infection was involved in the case of infection with influenza B. For blood-borne viruses, 92% of infections occurred in hospitals and 93% of these had percutaneous mode of infection, while among laboratory infections 77% were due to infective aerosol inhalation. Among blood-borne virus infections there were six cases of particular note: three cases of acute hepatitis following hepatitis C virus infection with a short period of incubation, one laboratory case of human immunodeficiency virus infection through aerosol inhalation, one case of hepatitis following hepatitis G virus infection, and one case of fulminant hepatitis with hepatitis B virus infection following exposure of the worker's conjunctiva to hepatitis B virus e antigen-negative patient saliva. Of the 12 infections with viruses with preferential mucocutaneous transmission, seven occurred percutaneously, aerosol was implicated as a possible source of infection in two cases, and one atypical infection with Macacine herpesvirus 1 with fatal encephalitis as the outcome occurred through a louse bite. One outbreak of norovirus infection among hospital staff had as its probable mode of infection the ingestion of inocula spread in the environment by fomites.

**Conclusions:** The currently accepted and practiced risk analysis of accidental viral infections based on the conventional dynamics of infection of the etiological agents is insufficient to cope with accidental viral infections in laboratories and to a lesser extent in hospitals, where unconventional modes of infection are less frequently present but still have relevant clinical and potential epidemiological consequences. Unconventional modes of infection, atypical clinical development, or extremely severe cases are frequently present together with high viral loads and high virulence of the agents manipulated in laboratories. In hospitals by contrast, the only possible association of atypical cases is with the individual resistance of the worker. Current standard precaution practices are insufficient to prevent most of the unconventional infections in hospitals analyzed in this study; it is recommended that special attention be given to flaviviruses in these settings.

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## 1. Introduction

Accidental viral infections among workers of hospitals or research laboratories are an emerging threat due to reasons among which stand out the growing volume of virological research done including with biohazard class 3 or 4 agents;<sup>1</sup> the emerging or reemerging viruses such as the severe acute respiratory syndrome coronavirus (SARS-CoV; epidemic of 2003), Marburg virus (MARV; the worst outbreak of MARV hemorrhagic fever took place in Angola in 2005), the reemergence of dengue hemorrhagic fever in the Americas in the 1980 s, the introduction of West Nile virus (WNV) in North America in 2000; and the global amount of hepatitis C virus (HCV) or human immunodeficiency virus (HIV) carriers (about 100 million and 40 million, respectively). This hazard has been increased by the concept of epidemiological transition that prevails in developed countries despite its clear refutation by the above data.

Hospitals and research laboratories are special environments with respect to the transmission of infection, given the modified susceptibility of the population present (larger proportion of immunocompromised individuals in hospitals, far greater vaccine coverage among workers than in the average population). The intensity and deepness of contact, and the concentration and invasiveness of the pathogens encountered are also higher than those found in conventional settings.

EpiNet (the Exposure and Prevention Information Network) statistics show 590 164 percutaneous and 196 721 mucocutaneous exposures to blood for health care workers in hospitals in the USA in 1996, 39% of these without notification.<sup>2</sup> This study evidenced an average of 5.4 percutaneous exposures of resident surgeons per year at a hospital in Toronto with a notification rate of only 5%,<sup>2</sup> supporting the above points about invasive exposure in hospitals.

An exceptional example of the unique character of the environments mentioned is the accidental release of infective aerosols containing weaponized *Bacillus anthracis* that occurred in Yekaterinburg in 1979. Seventy-seven persons became sick and 66 died from infections, the victims scattered over a 4.02 km radius. The source aerosols had an estimated mass ranging from milligrams to some grams.<sup>3</sup> The dispersion and stabilization power of the aerosol vehicle over the inoculum and the fundamental vulnerability of research laboratories to these particles as infective vehicles are evident given the frequency and the volume of aerosol generating procedures. These aerosol particles are liquid, solid, or mixed particulate bodies in suspension in a fluid (in this case air), whose size varies from 0.01  $\mu\text{m}$  to 10  $\mu\text{m}$ , hence being extremely light and able to remain in suspension for long periods of time.

The fundamental aims of this study were to establish and compare the modes of infection in accidental viral infections in research laboratories and hospitals, taking into account their presentations and their classification by conventional transmission mode, and the biosafety aspects involved.

## 2. Methods

This was a systematic review of articles published during the period 1930 to 2008. The inclusion criteria for the retrieved articles were the presence of an accidental viral infection in workers or students in research laboratories or hospitals and the presence of respective case reports. Exclusion criteria were the absence of the casuistics in the above thematic, the absence of the determination of the viral etiology, or the lack of at least a probable mode of infection.

The following academic Internet search systems were used: PubMed, Google Scholar, ISI Web of Knowledge, Scirus, and Scielo. They were searched with the keywords “virus laboratory infec-

tion”, “virus hospital infection”, “accidental virus infection”, “accidental infection by virus”, and their translations in Portuguese, German and Spanish. The references of the articles obtained were also used as sources. Previous articles available to the authors that met the inclusion criteria and were not eliminated by the exclusion criteria were also analyzed.

Percentages of infections by virus or virus groups respective to the various modes of infection were calculated and summary tables were produced.

## 3. Results

### 3.1. Search results

From the literature search, 141 articles were collected for the systematic review; 66 of these were selected for the analysis.<sup>4–69</sup> Those eliminated by fulfillment of the exclusion criteria are presented in the Supplementary Material. Of the 66 analyzed articles, 31 reported hospital infections, accounting for 241 of the infections analyzed. Thirty-five analyzed articles related 219 laboratory infections, including one article that reported both laboratory and hospital infections.

### 3.2. Description and analysis of the cases

#### 3.2.1. Arbovirus infections

Fifty arbovirus infections were analyzed of which 22 were caused by flaviviruses, 16 by alphaviruses, six by bunyaviruses (five by Crimean-Congo hemorrhagic fever virus (CCHFV) and one by Rift Valley fever virus (RVFV)), and six by Piry virus (vesiculovirus, *Rhabdoviridae*). Of the 50 cases, 38 occurred in laboratories and 12 in hospitals.

In one instance dating from 1935, a hospital infection with yellow fever virus (YFV) occurred through the mucocutaneous mode of infection, specifically exposure of the skin, which was reported to be unbroken, to the blood of a yellow fever patient. After 10 days, this health care worker developed fever and splenomegaly; 1 day later he developed jaundice and diarrhea, and subsequently petechiae, melena and delirium, with facial muscle contractions. On the following day, the worker died. The clinical picture of this exceptional case is consistent with yellow fever hemorrhagic fever.<sup>4</sup>

A case reported in 1939 concerns a laboratory infection caused by the western equine encephalitis virus (WEEV) percutaneously; the woman presented fever and headache 10 days after entering the laboratory and starting work with WEEV. Five days after the first symptoms, the fever peaked (40 °C) and convulsions progressing to coma and death on the following day overcame.<sup>5</sup> Another exceptional case of laboratory WEEV infection was reported in 1940 and occurred as a researcher had the mucosa of the facial cavities exposed to highly concentrated chicken embryo viral inocula and aerosol released in a centrifugation accident that dispersed visible viral inocula over a considerable extent of the laboratory room surfaces. The researcher had not been using goggles or a protection mask at the time of the accident. Fourteen days after the accident, the researcher presented headache, nausea, and vomiting, and 2 days later a fever of 39.4 °C. Manifestations of irritability, spasms of superior members' muscles, delirium and lethargy resulted in his hospitalization. The fever peaked at 42.2 °C and cardiac frequency reached 140 bpm, 8 days after first symptoms death occurred due to meningo-encephalitis.<sup>6</sup> The researcher's failure to use personal protective equipment was critical in his exposure to the inocula in the amount involved in this infection.

In 1943, eight cases of VEEV (Venezuelan equine encephalitis virus) infection occurred at a laboratory, for which the original

report pinpointed particles in suspension as the common source of infection. This report cited dust particles as the source and infective particle inhalation as the mode of infection.<sup>7</sup> The period of incubation ranged from 2 to 4 days, and the clinical presentation was of fever and biphasic headache, with cases considered as being normal to severe VEEV infections.

In four cases of VEEV infection at a laboratory, originally reported in 1947, aerosol inhalation was considered the mode of infection. Cases included a biochemist who worked in the room next to the virology work room, which he had never entered.<sup>8</sup> The virology work room was used for the production of viral stocks in chicken embryos, with high viral titers.

The two remaining alphavirus infections occurred in two laboratories in which aerosol inhalation was the mode of infection. The first was an infection of a researcher by chikungunya virus (CHIKV), which was originally reported in 1965.<sup>9</sup> In this instance a suspension of 10% infected mouse brain was used to infect mosquitoes through a nylon membrane. The researcher had had no direct contact with the viral suspension and was certified as having had no mosquito bites during the procedure, leaving only aerosol as the source of infection. Following 8 days of incubation the researcher presented with fever, muscular pain, and rash, and only lymphocytosis as a remarkable feature, being this a mild normal presentation of CHIKV infection.<sup>9</sup> The last case of alphavirus infection was a laboratory infection with Mayaro virus (MAYV) reported in 1999 in which the mode of infection was aerosol inhalation. This occurred during a sucrose–acetone antigen extraction procedure, followed by obtainment of solid antigen by dehydration with the use of a vacuum pump.<sup>10</sup> The infection with aerosol as source was demonstrated, and developed clinically following 6 days of incubation with fever and indistinct and mild clinical course, which is expected for normal MAYV infections.<sup>10</sup>

All 16 of these accidental infections by alphaviruses took place in laboratories and were predominantly caused by infective aerosol inhalation. The severity of the WEEV infections is of note, as this virus is considered less virulent than eastern equine encephalitis virus (EEEV) and VEEV in conventional natural infections.<sup>70</sup>

Of the total 22 accidental infections by flaviviruses analyzed, seven occurred in hospitals, one caused by YFV and the others caused by dengue virus (DENV). Two resulted from the mucocutaneous mode of infection (exposure of the worker's conjunctiva to blood of the patient with dengue fever, and exposure of another worker's skin to a small amount of blood from a yellow fever patient). The five remaining DENV infections had percutaneous mode of infection. For the 15 laboratory cases, the modes of infection were percutaneous in five cases and aerosol inhalation in 10.

The series of louping ill virus (LIV) accidental infections comprises two reports of three cases each. In the first, the mode of infection was only pinpointed for one case and was percutaneous with inoculation of a viral suspension of  $10^5$  mouse LD<sub>50</sub> (lethal dose 50%) × 0.03 ml (high viral titer). The clinical presentation followed 6 days of incubation and included fever, sore throat, neck swelling, severe headache, and vomiting, which resulted in hospitalization. The other two cases had biphasic meningo-encephalitis after 6 days of incubation, one of whom also presented ketoacidosis, coma, and conjunctival hemorrhage.<sup>11</sup> In the second report, two percutaneous infections and one with aerosol as source of infection were reported; the period of incubation ranged from 5 to 8 days (in the case of aerosol inhalation). In both percutaneous cases, fever, headache, and local lymphadenopathy occurred, while the aerosol case presented clinically with fever, retro-orbital pain, lack of coordination, nausea, and severe diarrhea. In this latter case viral suspensions with high viral titers were again handled, while the two percutaneous cases had worked with infected mice.<sup>12</sup>

Five laboratory infections of tick-borne encephalitis virus (TBEV) were reported, and the source of infection was established as aerosol for four of these cases;<sup>13–15</sup> the remaining case was excluded from further analysis. Two of the cases had a period of incubation of 10 days, with fatal meningo-encephalitis as the outcome for one and an inapparent infection in the other.<sup>13,14</sup> One of the remaining cases had aerosol inhalation as the probable mode of infection, but the report did not describe the clinical development.<sup>13</sup> The last case in this series occurred as a researcher processed a viral suspension of 10% infected mouse brain (high viral titer), with aerosol inhalation as the probable mode of infection. After 14 days of incubation, fever (40 °C), myalgia, arthralgia, and severe headache without neurological alterations manifested, comprising a normal clinical picture for TBEV infections.<sup>15</sup>

A laboratory infection with Saint Louis encephalitis virus (SLEV), with aerosol as the source of infection but no further details, is mentioned among a number of other accidental viral infections by Pike;<sup>16</sup> but like Hanson et al.<sup>13</sup> who described 424 laboratory arboviral infections, all but this one case were excluded from the analysis due to the absence of critical information as defined in the exclusion criteria.

Three cases of Kyasanur Forest disease virus (KFDV) laboratory infection with aerosol inhalation as the mode of infection were reported. The incubation period was 5 days, and was followed by conjunctivitis and mild respiratory symptoms in one case, myalgia, hyperesthesia and high viscosity of the skin in another case, and polyarthralgia, hyperesthesia and meningitis in the final case.<sup>17</sup> These presentations are consistent with the conventional clinical spectrum for KFDV.

There were three laboratory infections with WNV: one had infective aerosol inhalation as the mode of infection, while the other two had percutaneous mode of infection. The case due to aerosol inhalation had an incubation period of 5 days and then fever with a normal mild clinical outcome.<sup>16,18</sup> The two percutaneous infection cases had incubation periods of 3 to 4 days and fever with mild respiratory symptoms in one and fever with maculopapular rash in the other, all within the normal clinical range for WNV infections.<sup>19</sup>

The 12 accidental arboviral infections that occurred in hospitals analyzed in this study included seven as a result of the mucocutaneous mode of infection (one YFV infection, one DENV infection, and five CCHFV cases) and five by percutaneous mode caused by DENV, with the period of incubation ranging from 4 to 8 days and the development of classical dengue fever.<sup>4,20–24</sup> Three cases of RVFV infection occurring at a laboratory were reported in 1935.<sup>25</sup> The mode of infection was established as aerosol inhalation for only one of these cases. It must be pointed out that although the clinical development was of mild viral fever, the incubation period ranged from 30 to 90 days, while the normal incubation period for natural RVFV infection is up to 6 days.<sup>25</sup> The analyzed cases of CCHFV infection resulted from a single hospital cluster in which one patient presenting hemorrhagic fever due to infection with this virus was examined by a physician whose skin was exposed to bloody vomit during the procedure. After this mucocutaneous exposure, the physician developed fever, leukopenia, and hemorrhages consistent with hemorrhagic fever caused by this virus, and recovered 1 month later. The four remaining cases were exposed to the virus during a surgical procedure on the above mentioned patient, in which a surgeon and an assistant officer had close contact with the patient and an anesthetist and another member of the surgical team also had contact with the patient's blood. Hence the mode of infection was probably mucocutaneous, although the possibility of infective aerosol exposure from the patient's airways cannot be discounted. All four of these cases

**Table 1**

Summary table for accidental infections with arboviruses in the laboratory and hospital settings: total number of cases analyzed, overview of percentages according to the main modes of infection, and clinical development characteristics

Setting	Genus	Virus	Transmission route			Clinical development	Total number of cases	Ref.	
			Percutaneous	Aerosol exposure/inhalation	Mucocutaneous				
Laboratory	Alphavirus	WEEV	50	50 <sup>a</sup>	50 <sup>a</sup>	Lethal (100)	2	5,6	
		VEEV		100		Normal	12	7,8	
		CHIKV		100		Normal	1	9	
		MAYV		100		Normal	1	10	
		Total cases		6		94	6 <sup>a</sup>	(See above)	16
	Flavivirus	LIV	75	25		(See above) <sup>b</sup>	4	11,12	
		TBEV		100		Unapparent to severe	4	13–16	
		KFDV		100		Normal to severe	3	17	
		SLEV		100		Not described	1	13	
		WNV		66		33	Normal	3	16,18,19
		Total cases		33		66	(See above)	15	11–19
Phlebovirus (Bunyaviridae)	RVSV	66	100 <sup>c</sup>		Long incubation period	1	25		
	Vesiculovirus (Rhabdoviridae)		Piry		100	Normal	6	26	
	Total laboratory cases					(See above)	38	5–19,25,26	
Hospital	Flavivirus	DENV	83		17	Normal	6	20–23	
		YFV			100	Severe (lethal)	1	4	
		Total cases			71.5	28.5	(See above)	7	4,20–23
	Nairovirus	CCHFV	71.5		100	Normal (hemorrhagic fever in all, lethal in two cases)	5	24	
		Total hospital cases			41.6	58	(See above)	12	4,20–24

WEEV, western equine encephalitis virus; VEEV, Venezuelan equine encephalitis virus; CHIKV, chikungunya virus; MAYV, Mayaro virus; LIV, louping ill virus; TBEV, tick-borne encephalitis virus; KFDV, Kyasanur Forest disease virus; SLEV, Saint Louis encephalitis virus; WNV, West Nile virus; RVSV, Rift Valley fever virus; DENV, dengue virus; YFV, yellow fever virus; CCHFV, Crimean-Congo hemorrhagic fever virus.

<sup>a</sup> Refers to the same case.

<sup>b</sup> Comparison was impossible as there is no reference for the normal clinical development.

<sup>c</sup> Refers to the only case whose mode of infection was established.

presented hemorrhagic fever, with a fatal outcome for the surgeon and the assistant officer.<sup>24</sup>

The six reported laboratory accidental infections with Piry virus, a vesiculovirus (*Rhabdoviridae* family), had aerosol inhalation as the probable mode of infection. One of these cases had fever, myalgia, headache, and elevated transaminase levels.<sup>26</sup>

Among accidental arbovirus infections, 11 cases were the result of percutaneous infection and 32 had aerosol involvement. All of those with aerosol involvement took place in laboratories in a total of 38 analyzed cases of these settings; with the respective data presented in Table 1.<sup>4,11–26</sup> The DENV infections were an exception to the above general trend for accidental arbovirus infections, accounting for six of the hospital infections, including all the cases linked to the percutaneous mode of infection corresponding to 41.6% of the arboviral infections in these settings, as presented in Table 1. The DENV percutaneous cases constituted 45.4% of the total percutaneous arbovirus infections analyzed in this study.

### 3.2.2. Airborne viruses

A total of 197 cases of accidental infection with airborne viruses were analyzed. Of these, 160 occurred in laboratories and 37 in hospitals; 175 resulted from aerosol inhalation and 15 from droplet inhalation.

The series of reports of accidental infection with airborne viruses begins with two cases, one reported in 1942 and the other in 1943. Both were laboratory infections with lymphocytic choriomeningitis virus (LCMV). In the first case, the mode of infection was arthropod vectorization, as the infection resulted from the bites of lice from a dying infected monkey; this infection developed clinically with leukopenia, paralysis, and meningo-encephalitis.<sup>27</sup> The second case occurred upon the generation of infective aerosol due to the explosion of a celluloid tube submitted to a flame; the tube contained a suspension of 10% infected guinea pig spleen. After 17 days of incubation, this case presented clinically fever, dry cough, jaundice, leukopenia, and pneumonia.<sup>28</sup>

One case of Machupo virus infection was attributed to infective dust inhalation.<sup>13</sup> Three other cases of Machupo infection occurred in a hospital cluster. Two of the cases were nurses who cared for a patient with Bolivian hemorrhagic fever during the last 3 days of disease and life, in which the mode of infection was probably mucocutaneous, though there was also the possibility of infective aerosol involvement. The clinical presentation in one of these nurses was of classical Bolivian hemorrhagic fever, with 10 days of incubation followed by jaundice, necrotizing bronchopneumonia, hemorrhages, and death on the 12th day of illness. Clinically, the other nurse developed fever and nausea after 9 days of incubation and was hospitalized 6 days after, following which hemorrhagic fever presented; the nurse recovered on the 11th day of hospitalization. The third analyzed case in this cluster was a medical examiner who cut his thumb while performing an autopsy on the first nurse at 3-h post-mortem. He immersed the thumb in formalin, changed his gloves, and resumed the autopsy. After 4 days of incubation, fever (38 °C) manifested, with subsequent jaundice requiring the hospitalization of this case. Hemorrhagic fever then manifested and he died 5 days after hospitalization, with disseminated parenchymal necrosis and lung consolidation being found on pathological analysis.<sup>29</sup>

Another accidental infection case occurred through aerosol inhalation during initial works on the characterization of Sabia virus. This case presented with a 3–4-week period of incubation (a long period of incubation for a New World arenavirus) and a non-lethal hemorrhagic fever.<sup>30</sup> A second laboratory infection with Sabia virus and aerosol inhalation as the mode of infection occurred in a biosafety level 3 (BSL3) facility. Despite that, the researcher only wore a disposable gown, two pairs of gloves, and a surgical mask (droplet protection only), which constitute BSL2 personal protective equipment. The researcher had no positive pressure high efficiency particulate air (HEPA) filtered respirator, and after performing a centrifugation of 200 ml of viral suspension in a bottle with Vero cell culture (high titer viral suspension with



high volume), viral suspension was found in the bottom of the rotor and the outside of the bottle was wet when the lid of the rotor was opened by the virologist. After 8 days of incubation the researcher presented myalgia, neck stiffness, fever, and headache. On hospitalization, fever (37.6 °C), tachycardia (96 bpm), hematocrit of 42%, leukopenia, platelet count of  $138 \times 10^9/l$ , and moderate proteinuria were present, and intravenous ribavirin was administered for 9 days. On the second day of hospitalization the white blood cell count reached a nadir of  $1.3 \times 10^9/l$  and the platelet count was  $98 \times 10^9/l$ . No hemorrhages presented and the patient made a complete recovery after 10 days in hospital.<sup>31</sup>

Twenty-one LCMV infections with aerosol inhalation as the mode of infection occurred in a hospital; strikingly half of the cases developed only fever and myalgia, an extremely mild presentation for LCMV infections.<sup>32</sup>

The accidental infections with hantavirus in laboratories included 149 cases, of which 147 had infective aerosol inhalation as mode of infection. One hundred and twenty-six of the total hantavirus cases were infected with the B1 strain of Puumala virus (PUUV), of which two cases are of particular note: a case with percutaneous mode of infection due to an infected rat bite and a case of conventional percutaneous mode of infection, both of whom had hemorrhagic fever with renal syndrome (HFRS).<sup>33</sup>

Of the 14 cases of SARS, 13 occurred in hospitals with droplet inhalation as the mode of infection and an incubation period ranging from 2 to 7 days, followed by the development of typical pneumonia.<sup>34</sup> The remaining case occurred in a laboratory, had aerosol inhalation as the mode of infection, and had an atypical clinical development with only fever and minor upper respiratory symptoms.<sup>35</sup> The absence of droplet precautions, namely the use of surgical masks as primary personal protective equipment, was a critical factor in the SARS-CoV hospital infections.

The accidental hospital infections with airborne viruses retrieved and analyzed in this study are the LCMV infection cases of 1975,<sup>32</sup> the SARS cases of 2003,<sup>34</sup> and the Bolivian hemorrhagic fever of 1971 (Table 2<sup>13,27–39</sup>). An incomplete predominance of the conventional modes of infection is clearly shown in Table 2.<sup>13,27–39</sup>

### 3.2.3. Blood-borne viruses

The majority of accidental infections by blood-borne viruses analyzed in this study occurred in the hospital setting, with 152 cases from 17 references, in contrast with the 13 cases of laboratory infection from two references (Table 3).

The 13 cases in laboratories were caused by parvovirus B19 (nine cases), with the supposed mode of infection as aerosol inhalation and no further information on the infection event or the clinical outcome,<sup>40</sup> and HIV-1 (four cases). Among the 152 hospital cases analyzed, 142 involved the percutaneous mode of infection non-exclusively and 12 involved the mucocutaneous mode of infection non-exclusively (two of which involved inocula contact with the conjunctiva<sup>41,42</sup>). Of these 152 cases, 51 were caused by HCV, 91 by HIV (one of which was of simultaneous HIV and HCV infection), eight by parvovirus B19, two by hepatitis B virus (HBV; one of which was of simultaneous HBV and hepatitis D virus (HDV/delta virus) infection), and one by hepatitis G virus (HGV).<sup>42–47</sup> One case of HIV infection that occurred in a laboratory before 1988 is of great relevance, as the researcher suffered an infection with an in vitro culture-adapted strain of HIV-1 while working in BSL3 conditions carrying out viral stock production procedures. This infection was associated with repeated viral suspension spills inside the centrifuge and in the work area.<sup>46</sup>

Another noteworthy case was a fulminant hepatitis B case whose mode of infection was mucocutaneous due to contact of the nurse's conjunctiva with a hepatitis B e antigen (HBeAg)-negative HBV carrier patient's saliva. Such a case exemplifies an infection with exceptional severity given the low risk exposure involved once HBeAg is the main marker for the source patient's infectivity;<sup>42</sup> such an infection argues for the case of the relevance of susceptibility of the inoculated person. Another exceptional case was an accidental simultaneous infection with HCV and HIV by percutaneous mode of infection.<sup>43</sup> For the HCV the period of incubation was 44 days and was followed by mild acute hepatitis.<sup>43</sup> Three other HCV infection cases were remarkable due to the exceptionally short incubation periods following percutaneous infection. One of them had a period of incubation

**Table 2**

Summary table for infections with airborne viruses in the laboratory and hospital settings: total number of cases analyzed, overview of percentages according to the main modes of infection, and clinical development characteristics

Setting	Family	Virus	Mode of transmission					Clinical development	Total number of cases	Ref.
			Percutaneous	Aerosol exposure/inhalation	Droplet inhalation	Mucocutaneous	Oral			
Laboratory	Arenaviridae	LCMV	50	50				Normal to severe (meningo-encephalitis)	2	27,28
		Sabia		100				Normal	2	30,31
		Machupo		100				Not described (See above)	1	13
		Total cases	20	80					5	13,27,28,30,31
	Bunyaviridae	Hantavirus	1.3	98.7				Normal to severe (one death and one HFRS with DIC)	149	33,36,37
	Coronaviridae	SARS-CoV		100				Mild	1	35
	Orthomyxoviridae	Influenza B				100		Conjunctivitis (atypical)	1	38
	Picornaviridae	Coxsackievirus		50	25		25	Normal to atypical (one with nausea and diarrhea)	4	39
	Total laboratory cases		2	96	0.6	0.6	0.6	(See above)	160	13,27,28,30,31,33,35–39
Hospital	Arenaviridae	Machupo	33					Normal (lethal for two of the cases)	3	29
		LCMV		100				Extremely mild (See above)	21	32
		Total cases	4	88					24	29,32
	Coronaviridae	SARS-COV			100			Normal	13	34
		Total hospital cases	2.7	56.8	35.1	5.4		(See above)	37	29,32,34

LCMV, lymphocytic choriomeningitis virus; HFRS, hemorrhagic fever with renal syndrome; DIC, disseminated intravascular coagulation; SARS-CoV; severe acute respiratory syndrome coronavirus.

**Table 3**

Summary table for infections with blood-borne viruses in the laboratory and hospital settings: total number of cases analyzed, overview of percentages according to the main modes of infection, and clinical development characteristics

Setting	Family	Virus	Mode of transmission			Clinical development	Total number of cases	Ref.
			Percutaneous	Aerosol exposure/inhalation	Mucocutaneous			
Laboratory	Parvoviridae	Parvo-B19		100			9	40
	Retroviridae	HIV-1	75	25		Normal (seropositivity)	4	46
	Total laboratory cases			23	77	(See above)	13	40,46
Hospital	Retroviridae	HIV-1	98		2 (8) <sup>a</sup>	Normal	91 <sup>b</sup>	43,46
	Parvoviridae	Parvo-B19			100		8	44
	Flaviviridae	HCV	98		2	Normal to atypical (see Table 4)	51 <sup>b</sup>	41,43,48–57
		HGV	100			Unapparent	1	47
	Total cases		98		2	(See above)	52	41,43,47–57
	Hepadnaviridae	HBV	50		50	Normal to severe (one fulminant hepatitis)	2 <sup>c</sup>	42,45
	Deltaviridae	HDV	100			Normal (acute hepatitis after 90 days)	1 <sup>c</sup>	45
	Total hospital cases		93		7 <sup>d</sup>	(See above)	152	41–57

Parvo-B19, parvovirus B19; HIV, human immunodeficiency virus; HCV, hepatitis C virus; HGV, hepatitis G virus; HBV, hepatitis B virus; HDV, hepatitis D virus (delta virus).

<sup>a</sup> Two percent refers to cases of mucocutaneous mode of infection only, and 8% refers to simultaneous mucocutaneous and percutaneous modes of infection.

<sup>b</sup> Refers to a single case of simultaneous infection with HIV and HCV.

<sup>c</sup> Refers to a single case of simultaneous infection with HBV and HDV.

<sup>d</sup> Refers to cases with mucocutaneous mode of infection only.

of 13 days,<sup>48</sup> another had 9 days,<sup>49,50</sup> and the third had 2 weeks,<sup>50</sup> while the normal period of incubation for HCV is approximately 2 months;<sup>49</sup> these cases developed acute hepatitis.

Table 3<sup>40–57</sup> shows the clear predominance of the percutaneous mode of infection for HIV and HCV, but not for parvovirus B19 infections. The low number of HBV and HGV infections limits comparisons by their modes of infection (Table 3).

The cluster of eight cases of parvovirus B19 at a hospital, with the mucocutaneous mode of infection, shows the differentiated dynamics of this virus, with relevant involvement of fomites in the process given the evidence of widespread contamination of surfaces by the virus in the ward where the cases occurred.<sup>44</sup> The critical biosafety aspects for the occurrence of these infections were ineffective disinfection of the ward surfaces, insufficient changing of gloves, and inadequate hand disinfection, characterizing incomplete implementation of the standard precautions by health care workers.

Table 4 shows six cases that presented particularly dangerous situations: the three cases of acute hepatitis caused by HCV with periods of incubation far shorter than normally found and expected by health care workers, the case of fulminant hepatitis caused by HBV after exposure considered to be of insignificant risk by health care workers, one case of unapparent infection by HCV which causes hepatitis and still attracts little attention from health care workers, and one case of HIV-1 infection with an extremely unexpected mode of infection given the exceptional circumstances of the case, as described above.

### 3.2.4. Viruses with preferential mucocutaneous mode of infection

Until now, the mucocutaneous mode of infection has referred to contact between the mucosa and inoculum, yet among the viruses

mentioned below there are those that produce infection in contact with unbroken skin. The series of analyzed reports on infections with these viruses begins with two cases of infection with herpes B (Macacine herpesvirus 1; MCHV1) in laboratory settings. The first case occurred in 1932 and was caused by an infected monkey bite resulting in ascending myelitis and death. In the second case, a small skin injury came into contact with infected monkey saliva, resulting initially in a local herpetic lesion and then in a clinical outcome similar to the first case, with respiratory arrest and death within a few days.<sup>58</sup> One additional infection with herpes B (MCHV1) occurred by mucocutaneous mode of infection in a research laboratory setting. This case was exposed to unidentified secretions of an infected macaque in the eye. Ten days after this exposure the affected eye was swollen and red but without dendritic lesions, and 5 days later the worker presented fever (38.5 °C) and conjunctivitis and was hospitalized. Cerebrospinal fluid examination showed the presence of 8 lymphocytes/ml, and acyclovir (15 mg/kg) was administered from 2 h after hospitalization. The worker was discharged after 11 days on intravenous ganciclovir outpatient therapy; 1 day later the worker suffered ascending myelitis and subsequently flaccid paralysis. After the presentation of seizures, the clinical picture of postviral acute demyelinating encephalomyelitis was considered and this patient was then treated with foscarnet. Over the course of 9 days the patient developed nosocomial bacterial pneumonia, and died 33 days after the beginning of symptoms from refractory respiratory failure.<sup>59</sup>

A hospital infection with MARV occurred in a nurse following the repeated handling without gloves of wet facial tissues belonging to the companion of a patient with Marburg hemorrhagic fever. The patient with Marburg hemorrhagic fever died and

**Table 4**

Special cases of accidental blood-borne virus infection

Virus	Number of cases	Mode of infection	Clinical presentation	Ref.
HCV	3	Percutaneous	Short period of incubation (9 days to 2 weeks)	48–50
HGV	1	Percutaneous	Unapparent	47
HIV	1	Aerosol contact/inhalation	Seroconversion	46
HBV	1	Mucocutaneous	Fulminant hepatitis	42

HCV, hepatitis C virus; HGV, hepatitis G virus; HIV, human immunodeficiency virus; HBV, hepatitis B virus.

**Table 5**

Summary table for accidental infections with viruses with preferential mucocutaneous transmission in the laboratory and hospital settings: total number of cases analyzed, overview of percentages according to the main modes of infection, and clinical development characteristics

Environment	Family	Virus	Mode of transmission			Clinical development	Total number of cases	Ref.
			Percutaneous	Aerosol exposure/inhalation	Mucocutaneous			
Laboratory	Herpesviridae	McHV1	66		33	Normal	3	58,59
	Orthopoxviridae	VACV	50		50 <sup>a</sup>	Normal	4	61–64
	Arenaviridae	Lassa		100 <sup>b</sup>		Normal	1	16,65
	Total laboratory cases			50	12.5	37.5		8
Hospital	Herpesviridae	HSV-1	100			Normal	1	68
		HZV	100			Normal	1	67
	Arenaviridae	Lassa	100			Normal	1	66
	Filoviridae	MARV			100	Atypical mild (uveitis and thrombocytopenia)	1	60
	Total hospital cases			75		25		4

McHV1, Macacine herpesvirus 1; VACV, vaccinia virus; HSV-1, herpes simplex virus 1; HZV, herpes zoster virus; MARV, Marburg virus.

<sup>a</sup> Possible involvement of aerosol as source in one case of mucocutaneous mode of infection.

<sup>b</sup> Possible contact with infected secretions in addition to infective aerosol exposure.

then the companion manifested the same disease, hence this infection probably occurred through the mucocutaneous mode of infection. The nurse developed retro-orbital pain, myalgia, and fever (37.5–38.5 °C) and was hospitalized; 2 days later a low platelet count of  $49 \times 10^9/l$  and diarrhea presented. On day 5 of hospitalization a maculopapular rash was present on the arm and 2 months later the nurse developed uveitis, after which a full recovery was made. During the hospitalization period MARV was isolated from a sample of the liquid from the anterior ocular chamber.<sup>60</sup> The lack of contact precautions and use of barrier personal protective equipment were critical factors in this infection, as is commonly found in African hemorrhagic fever virus infections in health care workers.

Three cases of vaccinia virus (VACV) infection in laboratory settings stand out: the first case occurred as a result of percutaneous infection by two recombinant strains, one containing the G gene and the second the 22-k gene, both from respiratory syncytial virus; this case developed more severely, with an incubation period of 3 days, followed by local tumor, rash, erythematous papules, and severe lymphadenopathy.<sup>61</sup> The second case happened with direct contact between the skin and the inoculum. The agent was a recombinant strain containing the cytohesin 1 gene whose product inhibits the biochemical cascade triggered by the binding of lymphocyte function-associated antigen (LFA-1) to intercellular adhesion molecule 1 (ICAM-1), therefore inhibiting inflammatory cell migration. Clinically, this case presented a local hemorrhagic necrosis in one exposed finger and a papule on the other exposed finger.<sup>62</sup> The third case of VACV infection occurred as a student processed a viral suspension of  $10^{10}$  PFU/ml (high titer), and the most likely mode of infection identified in this report was mucocutaneous, with viral particles carried by the hands to the eyes; alternatively there was the possibility that the eyes were exposed to infective aerosol. The clinical result of the infection was classical purulent ocular vaccinia.<sup>63</sup> The likelihood of inoculum carried by hands to the eyes constitutes a clear breach of adequate laboratory procedures and demonstrates the absence of use of personal protective equipment (goggles) as a factor in the occurrence of the infection.

Of a total of 12 cases of accidental infection with viruses of preferential mucocutaneous mode of infection, only four took place in the hospital setting. Of these, one was a case of Lassa virus infection reported in 1970, one was caused by MARV, another was a herpes zoster virus (HZV)<sup>67</sup> infection with percutaneous mode of infection that developed clinically as zoster after 2 days of incubation, and one was a herpes simplex virus 1 (HSV-1; now

named HHV-1, human herpes virus 1) percutaneous infection that developed as herpetic whitlow 4 days after a needlestick injury to the finger with a contaminated 22-gauge needle.<sup>68</sup> Table 5 shows that the percutaneous mode of infection has equal if not higher importance than the mucocutaneous mode, the conventional mode, an expected fact for both types of setting. The clinical outcomes of these cases were within the normal expected range for the respective agents, but they were severe, as the causative agents were highly virulent with the exception of HZV and HHV-1.

### 3.2.5. Orally transmitted viruses

Only one report was retrieved of an outbreak among health care workers at a hospital with 36 infections by a novel norovirus so denominated Basel-NOV (Basel Norwalk-like virus). In this outbreak no contaminated water or food was detected, but significant deviation from standard precaution procedures was found through the 'hazard analyses of critical check points' (HACCP) methodology. The supposed chain of transmission was initiated and mediated by fomites as the primary contaminant of hands that then carried inocula to the mouths of the infected persons.<sup>69</sup> The incubation period of the clinical cases was 3 days followed by fever, vomiting, and diarrhea, a typical clinical picture for norovirus infections.

### 3.2.6. Chronological evolution of the reports of accidental viral infection

The first analyzed report of accidental viral infection was published in 1935<sup>25</sup> and the last in 2006.<sup>63</sup> This period is divided into three intervals: the first comprising the period 1935–1958, the second 1959–1982, and the third 1983–2006.

For the first 24 years, 28 reported cases were analyzed, all in laboratories,<sup>5–8,14,25,27,28,32,39,58</sup> 20 of which were caused by arboviruses and six by airborne viruses.<sup>27,28,39</sup> Infective aerosol was the source of infection in 22 cases, 19 of which were arbovirus infections. Only two infections resulted from the percutaneous mode of infection: one herpes B<sup>58</sup> (currently named McHV1)<sup>71</sup> infection due to an infected monkey bite and one possible self inoculation of WEEV with a syringe.<sup>5</sup>

For the second 24-year period, 68 cases were studied, of which 31 occurred in hospitals (21 with involvement of infective aerosols, three percutaneous, and seven mucocutaneous) and 37 occurred in laboratories (31 with involvement of infective aerosols and four through the percutaneous mode of infection, one of which was a possible percutaneous mode combined with infective aerosol inhalation). Within this period, six cases were caused by LIV (three



through percutaneous mode of infection, one through aerosol inhalation, and the remaining cases through an unidentified mode of infection<sup>11,12</sup>), three were caused by KFDV due to infective aerosol inhalation in laboratory settings,<sup>17</sup> five were caused by CCHFV in a hospital with probable mucocutaneous mode of infection,<sup>24</sup> three were caused by Machupo in a hospital,<sup>29</sup> 21 were caused by LCMV (all in a hospital through aerosol inhalation),<sup>32</sup> 25 by Hantaan hantavirus (HTNV) with aerosol inhalation as mode of infection,<sup>36,37</sup> one by TBEV with aerosol as source,<sup>13,16</sup> one by SLEV with aerosol as source,<sup>13</sup> one by Machupo virus in a laboratory,<sup>13</sup> and two by Lassa virus (one possibly through percutaneous mode of infection and one with mucocutaneous and possible aerosol inhalation as the mode of infection).<sup>65,66</sup>

The final 24 years comprised reports of 367 analyzed cases, of which 157 occurred in laboratories and 210 in hospitals. Of the cases in the laboratory setting, 145 involved infective aerosols, and 124 of these were caused by PUUV hantavirus,<sup>33</sup> one by SARS-CoV,<sup>35</sup> nine by parvovirus B19,<sup>40</sup> one by MAYV,<sup>10</sup> two by Sabia virus,<sup>30,31</sup> one by TBEV,<sup>15</sup> six by Piry,<sup>26</sup> and one by HIV-1.<sup>43</sup> The laboratory cases in this period are reported in 13 references. During this period 210 hospital infections were analyzed and reported in 26 references; 148 cases had a percutaneous mode of infection, none were due to infective aerosols, 13 SARS cases were due to droplet inhalation,<sup>34</sup> 13 involved the mucocutaneous mode of infection, and 36 cases of Basel-NOV infection supposedly occurred through the oral mode of infection.<sup>69</sup>

### 3.2.7. *Relevant factors to accidental infection in the laboratory or hospital setting*

Of the 219 analyzed cases that took place in research laboratories, 197 had aerosol as the source of infection, with aerosol inhalation the mode of infection involved in 84% of laboratory infections by arboviruses (94% of infections by alphaviruses). This mode of infection was also implicated in 77% of laboratory infections by blood-borne viruses and in 12.5% of laboratory infections by viruses of preferential mucocutaneous mode of infection. In laboratories, the percutaneous mode of infection was found for 15.7% of the infections by arboviruses (33% of the laboratory infections by flaviviruses), with this mode of infection also involved in 23% of infections by blood-borne viruses, in 2% of infections by airborne viruses, and in 50% of infections by preferential mucocutaneous transmission viruses. A total of 16 laboratory infections had the percutaneous mode of infection.

Among the 241 cases in the hospital setting, 151 had the percutaneous mode of infection; this mode of infection was involved in this setting in 41.6% of arbovirus infections, 92% of blood-borne virus infections, 3% of airborne virus infections, and in 75% of the cases of preferential mucocutaneous transmission virus infections. Of the total hospital infections, 27 had the mucocutaneous mode of infection (eight of these were caused by parvovirus B19 and seven by HIV, of which five also had percutaneous mode of infection involvement). This mode of infection was also possibly involved in 19 reported HCV accidental infection cases.<sup>54</sup> Seventeen of the 27 cases were caused by blood-borne viruses – a total 11% of the accidental infections caused by these viruses in hospitals. Of the total analyzed accidental hospital infections, 21 had aerosol inhalation as the mode of infection, all caused by LCMV. The remaining airborne virus infections in hospitals were caused by SARS-CoV following infective droplet inhalation, and Machupo virus with percutaneous or mucocutaneous mode of infection. Fifteen percent of hospital infections had the oral transmission mode and occurred in a single outbreak of Basel-NOV.

As expected, the percutaneous mode of infection was found to predominate in the hospital setting, with this mode relevant in cases of arbovirus infections and infections by viruses of preferential mucocutaneous mode of infection. The relationship

between the severity of the source case and the probability of accidental infection is well established,<sup>2</sup> but only a few analyzed cases support this association, and the case of fulminant hepatitis caused by HBV mucocutaneously is a noteworthy exception to that potential correlation trend. The occurrence of atypical or exceptionally severe cases in hospital settings, although rare, is not insignificant, with eight cases (3.3% of hospital infections) having no detectable correlation of their occurrence with any of the factors analyzed in this study.

## 4. Discussion

This study reveals unexpected patterns for accidental infections in laboratories and dangerous exceptions to the supposed dynamics of transmission in accidental infections in hospitals, demonstrating the limitation of the real knowledge of the dynamics of accidental infections in these settings. With regard to the pattern of laboratory infection, this study establishes a clear predominance of aerosol inhalation as the mode of infection, with involvement in 96% of airborne virus infections, 84% of arbovirus infections (in which stand out the alphaviruses for which 94% of infections involved this mode, and Piry with 100% of the infections by this mode), 77% of the infections by blood-borne viruses (parvovirus B19 in particular deserves attention as 100% of the laboratory cases had this mode of infection), and 12.5% of the infections by viruses with preferential mucocutaneous mode of infection. In contrast, the percutaneous mode answered for only 7.3% of the total analyzed laboratory infections. Paradoxically this mode of infection was involved in 50% of infections by viruses with preferential mucocutaneous infection and in 23% of those by blood-borne viruses, and also in 16% of arbovirus infections. Among these arbovirus infections, the flaviviruses stand out with regard to the involvement of this mode of infection (33% of the infections in laboratories).

Analysis of the percutaneous mode of infection in arbovirus infections had unexpected results given the two percutaneous infections by WNV reported in 2002,<sup>19</sup> and the difference between the percentages of flaviviruses and the entire viral group, 45% of arbovirus infections through this mode were caused by DENV (all between 1998 and 2004).<sup>20–23</sup> Apart from these results, the description of cases of WNV infection due to blood transfusion and organ transplantation<sup>72</sup> despite the fact that the human is still considered the terminal host in the conventional transmission chain for this virus,<sup>73</sup> the growing number of HCV infection carriers, and the discovery in 1995<sup>74</sup> of HGV and its addition to the group of blood-borne viruses causing hepatitis, point to the evolutionary possibility of certain flaviviruses becoming adapted to the percutaneous mode of infection as an effective mode of transmission.

The preponderance of the percutaneous mode of infection in hospitals is demonstrated by the proportion of cases with involvement of each mode; 62.6% of accidental infections in hospitals were through percutaneous mode, while aerosol inhalation was the mode of infection involved in a cluster of LCMV infections accounting for 8.7% of the cases in hospitals. In comparison, inhalation of infective droplets was involved in 13 SARS cases, accounting for 5.4% of the cases in hospitals, and a cluster of norovirus infections in a Swiss hospital<sup>69</sup> through oral mode of infection accounted for 15% of the analyzed cases in the hospital setting. In this study, only one cluster of accidental infections with aerosol inhalation as the mode of infection in a hospital was obtained from one report; this is probably a result of the difficulty of conducting epidemiological surveys of such infections, likely leading to sub-notification of cases.

The comparison of the three time-periods in which the analyzed reports were published clearly refutes the idea of a

preponderance of percutaneous infection in the first period and a decrease in the importance of this mode of infection in laboratory infections over time due to the methodological transition from *in vivo* infection models to *in vitro* culture systems in virological research. The number of analyzed cases has consistently grown through these periods, the first period did not include any hospital cases, and there were more references and cases in the last period than in the first two put together, due mainly to hospital case reports. These data support the idea of a decreasing sub-notification over time, and there are two reasons for these results: the first two periods correspond to the time of discovery and early characterization of many of the analyzed viruses, whereas the last period is marked by the development of the biosafety concept, resulting in a greater number of notifications. Moreover, the volume of virological research and the number of patients with viral diseases in hospitals have both grown over time. There is a uniformity in the laboratory viral infections profile respective to the mode of infection over time; remarkably only two of the percutaneous infections in laboratories were reported in the first period. There are two complementary conclusions that can be derived from these data: (1) there is no sub-notification bias specific to specific modes of infection over time, which was unexpected, and (2) the measures and protocols of biosafety generated to minimize the number of these accidental infections involving specific modes of infection were less effective than commonly supposed. In addition the majority of percutaneous infections in the hospital setting during the last period occurred with syringes after completion of the necessary procedure in the patient and even during needle recapping, demonstrating clear suboptimal implementation of the universal precautions, contact precautions, body fluid isolation, and standard practices of infection control.

The main risk factors for accidental viral infections in research laboratories are shown by the preponderance of work with high viral loads in reports of infections due to infective aerosol inhalation, with centrifugation as commonly present methodology in these. Also 15 of 21 first infections by arboviruses with aerosol involvement occurred during work with infected animal tissue suspensions. Another evident risk factor is the virus being handled, not only this study demonstrates that Piry, WEEV, TBEV, and alphaviruses in general are peculiar with respect to the risk of productive infection upon inoculation through aerosol inhalation, as the clinical severity of an infection by non-conventional mode of infection is clearly virus-orientated as displayed in WEEV, TBEV, MCHV1 infections, with a smaller contribution of host resistance for the clinical presentation and outcome.

Different risks are reported in hospitals, with mainly percutaneous exposure reported, followed by respiratory exposures (aerosols and droplet inhalation), oral exposure (one norovirus outbreak from one reference – extrapolation of the respective data to the general context is not appropriate), and mucocutaneous exposures, which in this study are correlated with 11.2% of the analyzed accidental hospital infections. However such results are likely the product of a sub-notification bias, as blood-borne viruses are the most frequently diagnosed hospital infections and these are the leading etiologies for infections by this mode of infection. No consistent correlation analysis could be pursued for the probability of infection or its severity and the deepness of the exposure with regard to the modes of infection analyzed. Even a comparison for the percutaneous and mucocutaneous modes of infection was not feasible due to the lack of data with respect to the deepness of exposure variable in a significant portion of the reports; this limitation hampered such a comparison even for those cases with the percutaneous mode of infection. Similarly comparison between the inocula in different cases for different modes of infection was not feasible due to the limitations in the data with

regard to the quantity of infective aerosol and droplets. Even the data on inocula in percutaneous infections are limited. The best approach for the issue is to use the clinical state of the source patient as a parameter for the inocula. Such an approach gave positive associations in the case of simultaneous HIV and HCV accidental infection,<sup>43</sup> in the case of Lassa hemorrhagic fever,<sup>16,66</sup> and in a case of dengue fever caused by mucocutaneous exposure for which the source patient presented secondary DENV infection with hepatitis and signs indicative of dengue hemorrhagic fever.<sup>23</sup> However the case of fulminant hepatitis by HBV<sup>42</sup> and the lack of data even in percutaneous case reports supporting this notion decrease support for this idea. The atypical or exceptionally severe infections in hospitals do not correlate with the mode of infection or the viral agent involved, and neither a greater deepness of exposure nor higher inocula were reported for these infections. Therefore, although the potential contribution of these factors cannot be ignored, the relevance of the individual host resistance as a factor for the occurrence of such cases is well supported in the hospital setting, whereas the relevance of this factor in such processes is lower in laboratory settings, as supported by the results and analyses presented herein.

The accidental infection risk dynamics for research laboratories is dominated by infective aerosols and, to a lesser extent, percutaneous infections, especially when the work involves infected animals. In this context the need for minimization of aerosol release and dispersion is clear, and therefore the global adoption of aerosol release minimization procedures is recommended, with emphasis on centrifugation and homogenization procedures, the adoption of adequate directional ventilation systems, and the use of personal protective equipment able to reduce aerosol exposure, such as N95 masks in areas of greater risk, even in BSL2 settings are also recommended. In order to target percutaneous exposures, complete training in the correct usage of needles and sharps should be provided, the use of two pairs of gloves is recommended, needlestick-prevention devices should be used, and even the number of samples or animals to be processed per batch should be limited in a given procedure.

With regard to hospital dynamics, the main risk to be diminished is percutaneous exposure, followed by respiratory and mucocutaneous exposure. Hence an expansion of the current standard precautions is advisable. Strongly recommended are the use of needlestick-prevention devices and the use of two pairs of gloves, with the outer pair being changed whenever the current standard precautions require the gloves to be changed. The use of a mask and goggles is also recommended whenever dealing with a feverish patient or whenever there is any reason to suspect a viral infection, particularly a blood-borne viral infection. N95 masks are highly recommended when treating patients with severe respiratory signs or in cases of hemorrhagic fever, and isolation is recommended in these cases, especially the latter. Definitive laboratory diagnosis and identification of the etiology should be sought when dealing with viral infections, especially the acute and potentially lethal ones. Of the eight analyzed cases whose mode of infection was completely unexpected (five percutaneous, one mucocutaneous by DENV, and one mucocutaneous by YFV) and whose clinical development was exceptionally fast and severe (fulminant hepatitis by HBV with mucocutaneous infection), two of the dengue cases (the mucocutaneous infection and one percutaneous due to deep puncture) would have been avoided by the strict adoption of standard precautions and three cases would have been avoided if not only the standard precaution protocols but also precautionary principle awareness had been in effect. This basic principle of biosafety is here interpreted as follows: total control of all the variables of a complex system is not possible at any given time, therefore the adoption of risk minimization and contingency measures against damages are

needed, with reasonable criteria, even when the specific risks under evaluation are considered insignificant a priori.

Emphasizing this last point there are reports related to laboratory and hospital cases of lethal outcome or high epidemiological risk presented by isolation and characterization of Lassa virus, MCHV1, and Sabia virus.<sup>30,58,65,66</sup> The risk of contact with viral human pathogens never before known to man is still present, and is possibly increasing, as demonstrated by the linear curve describing the discovery of new viruses through time from 1908 to 2008; the plotting of such a regression curve predicts the discovery of between 10 and 40 new viruses up until 2020,<sup>74</sup> with no forecasts of the virulence of such pathogens.

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