



Nipah virus: A review on epidemiological characteristics and outbreaks to inform public health decision making

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ABSTRACT

The objectives of this review were to understand the epidemiology and outbreak of NiV infection and to discuss the preventive and control measures across different regions. We searched PubMed and Scopus for relevant articles from January 1999 to July 2018 and identified 927 articles which were screened for titles, abstracts and full texts by two review authors independently. The screening process resulted in 44 articles which were used to extract relevant information. Information on epidemiology of NiV, outbreaks in Malaysia, Singapore, Bangladesh, India and Philippines, including diagnosis, prevention, treatment, vaccines, control, surveillance and economic burden due to NiV were discussed. Interdisciplinary and multi sectoral approach is vital in preventing the emergence of NiV. It is necessary to undertake rigorous research for developing vaccines and medicines to prevent and treat NiV.

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Introduction

Nipah virus (NiV) infection is also called as Nipah virus encephalitis and forms a new genus Henipavirus in sub family *Paramyxoviridae* [1]. The first NiV was isolated and identified by Dr. Kaw Bing Chua in 1999 after an encephalitis outbreak among pig farmers and exporters in Malaysia and Singapore, causing a collapse of the billion-dollar pig export industry [2]. Initially, the spread of infection could not be controlled as measures were targeted to control Japanese Encephalitis (JE) outbreak, until the isolation of NiV from cerebrospinal fluid of a victim after a period of 2 months, [3]. The virus was named after a village Kampung Sungai Nipah where it was first found [1]. NiV outbreaks in Malaysia and Singapore were followed by 2001 and 2007 outbreaks in India and Bangladesh (8 outbreaks from 2001 till 2012) [4]. The latest outbreak was reported on 19th May 2018, in Kozhikode district, Kerala, India [4].

Natural reservoir of NiV has been identified as fruit bats of the genus *Pteropus*. This disease can infect both humans and animals, like pigs, equally and the modes of transmission are: human to human transmission and animal to human transmission through infected bats and pigs [4]. The only method to address this highly fatal and contagious disease is to provide prompt symptomatic

treatment [5]. Case fatality rate of NiV infection is very high. Hence, knowledge about epidemiological aspects of NiV disease is imperative for planning future preventive, control and intervention measures. Also, there is a need to understand the epidemiology of NiV outbreaks and measures taken to control them, globally; which will help in adopting early effective measures to control future outbreaks. Therefore, this epidemiological review outlines determinants, modes of transmission, source of infection, types of reservoir, preventive and control measures and NiV outbreak patterns in different affected countries.

Methods

We searched PubMed and Scopus databases for relevant English language articles, from January 1999 to July 2018. Search strategy was developed using relevant keywords, mentioned in appendix I. Results were exported to citation manager—Zotero and Microsoft Excel after removal of duplicates. Search results were systematically screened for methodological articles during title, abstract and full-text screening, independently. All types of scientific articles were included to collate the findings on NiV infection.

Results

The literature search on two databases yielded 927 potentially relevant articles with 303 duplicates. Finally, 44 articles were included for extracting information on NiV as depicted in Supplementary Appendix 1.2.

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Table 1
Different diagnostic techniques developed in various labs.

Technique	Place
Rapid immune plaque assay for the detection of Nipah virus and anti-virus antibodies	CSIRO, Australia
Solid-phase blocking ELISA (enzyme-linked immunosorbent assay) for detection of antibodies to Nipah virus	DVS, Malaysia
Real-time Reverse transcription polymerase chain reaction (RT-PCR) (TaqMan)	Institut Pasteur, France
MAb (Monoclonal Antibodies) against formalin-inactivated NiV	National Institute of Animal Health, Japan.
Recombinant nucleocapsid protein produced in <i>Escherichia coli</i>	University Putra, Malaysia
MAB-based immunohistochemical diagnosis NiV	National Institute of Animal Health, Japan
Recombinant glycoprotein produced in insect cells	University Putra, Malaysia
Recombinant nucleocapsid protein produced in insect cells	University Putra, Malaysia
Recombinant glycoprotein produced in <i>E. coli</i>	University Putra, Malaysia
Monoclonal antibodies against NiV (4 MABs against “N” protein and 1 against “M” protein)	NCFAD (National Centre for Foreign Animal Disease), Canada
Indirect ELISA for the detection of Henipavirus antibodies based on a recombinant nucleocapsid protein expressed in <i>E. coli</i>	Chinese National Diagnostic Centre for Exotic Animal Diseases
Indirect IgG ELISA for human and swine sera and an IgM capture-ELISA for human sera using the recombinant NiV-N protein as an antigen	Institute of Tropical Medicine, Japan
Neutralization assays for differential Henipavirus serology using Bio-Plex Protein Array Systems	CSIRO, Australia
Duplex nested RT-PCR for detection of Nipah virus RNA (Ribonucleic acid) from urine specimens of bats	Chulalongkorn University Hospital, Thailand
Monoclonal antibodies against the nucleocapsid proteins	Institute of Veterinary Sciences, China
Neutralization test for specific detection of NiV antibodies using pseudo typed VSV (Vesicular stomatitis virus)	National Inst. Inf. Diseases, Japan
Recombinant matrix protein produced in <i>E. coli</i>	University Putra Malaysia, Malaysia
Neutralization assay using VSV pseudo type particles expressing the F and G proteins of NiV as target antigens	CDC, Atlanta
MAB based antigen capture ELISAs for virus detection and differentiation between NiV and Hendra Virus	CDC, Atlanta
Antigen capture ELISA using polyclonal antibodies obtained by DNA (Deoxyribonucleic acid) immunization	National Institute Inf. Diseases, Japan
Second generation of pseudo type-based serum neutralization assay for NiV antibodies	National Institute Inf Diseases, Japan

Source: [1].

Epidemiology

Host

Pteropus fruit bats are considered to be the natural host of NiV infection and are more commonly found in South East Asian & African countries. The reactive and neutralizing antibodies to NiV were detected in Pteropus fruit bats of Malaysia, Cambodia, Thailand, India, Bangladesh, and Papua New Guinea and non-Pteropid bats of Madagascar, Ghana, and China [6]. NiV has potential to cause infection that can be fatal in horses, pigs, cats, dogs, ferrets, hamsters, guinea pigs, monkeys, and humans [7].

Modes of transmission

NiV outbreak in Malaysia occurred during 1998–1999 due to the spillage of NiV from bats to pigs after consuming half eaten-fruits by bats [8]. Initially, the outbreak was misapprehended as JE, but later the source of infection was recognized as close contact with infected pigs and subsequent transmission to humans. [6,8–11]. Infection also spread to pig handlers in Singapore, as pigs were imported from Malaysia [8].

First outbreak in Bangladesh occurred in 2001, where north-western and central parts of the country were affected due to date palm sap consumption and person-to-person transmission [8,12]. An investigation suggested, washing infected corpse before burial according to Islamic rituals could have transmitted infection to family members [13]. Other risk factors such as contact with domestic animals and tree climbing demonstrated fewer chances of spreading infection [14].

In India, the initial NiV outbreak occurred in Siliguri, West Bengal (2001). Investigations suggested person to person transmission via respiratory secretions [8,15]. In the 2018 outbreak of Kerala, fruit bats were found as the source of NiV infections, confirmed by Indian council of Medical Research (ICMR) [16].

Clinical features

The median incubation period in case of raw date palm sap consumption was 10 days while in case of exposure to pigs, it ranged from 4 days to 2 months [1,17]. Majority of the patients show symptoms related to central nervous system, but respiratory pathology has also been reported [1,16,18]. Main presenting features of NiV

infection are acute encephalitis with fever, dizziness or vomiting; more than half of the infected cases presented reduced level of consciousness or prominent brain stem dysfunction in Singapore [1]. Similar features were also seen during the Kerala outbreak, India [16]. Neurological signs such as behavioral changes, spasms, uncoordinated gait and myoclonus were reported in patients from Bangladesh [8]. Cough was the commonly presented respiratory symptom, while atypical pneumonia was reported in 14% cases in Malaysian outbreak [1,8,19]. Complications of infection included acute or late onset encephalitis and associated disorientation or coma [20]. Viral bronchopneumonia, acute respiratory distress syndrome and myocarditis were also reported during the Kerala outbreak [16].

Environmental factors

Interactions between animals, humans and environment played a significant role during NiV outbreaks among South Asian countries [16,21]. There are multiple reasons for human-animal interactions like prolonged droughts, reduced animal habitats due to deforestations, anthropogenic forest fires in Indonesia and pig farming mixed with agriculture [10,22]. Deforestation and urbanization results in destruction of bat habitats which triggers them to invade human habitats for food. Hunger increases stress level and weakens immune system of bats due to which there is an increase in the viral load in their systems spilled out through secretions such as urine, semen or saliva [20]. “One Health approach i.e. “an approach to designing and implementing programmes, policies, legislation and research in which multiple sectors communicate and work together to achieve better public health outcomes” [23] was stressed during NiV outbreak to attain global health security by mitigating the effects caused by deforestation and urbanization [20].

Increase in virus shedding can also be associated with seasonal preferences. A study conducted in Thailand demonstrated an elevated viral load between April–June, correlating with the time period when young bats begin to fly. It has also been reported that all outbreaks occurred during December to May (winter and spring season) in Southeast Asia [20].

Table 2
Case fatality rate of NiV infection during outbreaks in different countries from 1999–2018.

Country	Year	Reported human cases	Reported deaths	Case fatality rate (%)
Malaysia	1998–1999	265	105	39.6
Singapore	1999	11	1	9.1
Bangladesh	2001	13	9	69.0
India	2001	66	45	68.0
Bangladesh	2003–2007	109	77	70.6
India	2007	5	5	100.0
Bangladesh	2008–2012	87	74	85.1
India	2018	19	17	89.0

Source: [4,16].

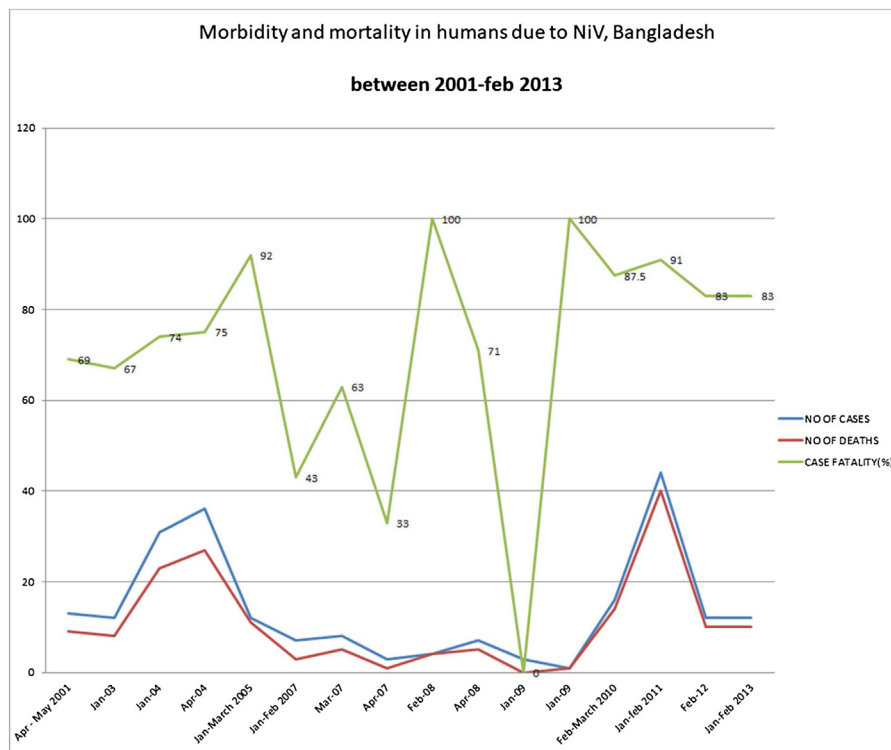


Fig. 1. Graph showing number of cases, deaths and case fatality rate in Bangladesh.

Source: [1].

Outbreaks

NiV outbreaks in various countries, starting from 1999, have led to high number of fatalities among humans. Case fatality rate (Table 2) and country-wise sequence of events during the outbreaks is given below:

Malaysia

Febrile encephalitis cases were reported among pig farmers in September 1998. Initial deduction was JE, vaccine imported from Japan was administered to farmers and people in close contact to pigs. By the end of 1998 only four of 28 samples were tested positive for anti-JE IgM, also, the virus could not be isolated from postmortem brain tissue of patients. Due to devastating effect of the outbreak, on 9th March, 1999 the presence of a novel virus was announced by the ministries of health and agriculture. Subsequently, the virus was named as Nipah, after the village from where the virus was first isolated, Kampung Sungai Nipah [24]. The outbreak began near Ipoh among pig farmers and spread to other major pig rearing areas, resulting in 265 human cases including 105 deaths [1,24,25].

Singapore Eleven cases and one death among pig abattoir workers was reported in Singapore between 10–19 March, 1999, due to

contact with live pigs imported from Malaysia during NiV outbreak period [24,26].

Bangladesh

First NiV outbreak was identified in Meherpur district of Bangladesh between April–May, 2001. Thereafter, districts affected by NiV infection between January 2003 to February 2013 were: Naogoan, Rajbari, Faridpur, Tangail, Thakurgaon, Kushtia, Pabna, Natore, Naogaon, Manikgonj, Rajbari, Faridpur, Gaibandha, Rangpur, Nilphamari, Madaripur, Gopalganj, Lal Mohirhat, Dinajpur, Rangpur, Comilla, Joypurhat, Rajshahi, Gaibandha, Rajshahi, Pabna, Jhenaidah and Mymensingh. Few districts of Bangladesh observed repeated outbreaks [1]. A total of 209 human cases of NiV infection were reported in Bangladesh from April 2001 to March 31, 2012, of which 161 (77%) died [20]. In 2001, 13 cases were diagnosed followed by multiple outbreaks until 2013, with 193 reported cases. Fatality rate in 2001 was 69% and in 2013 it increased to 83% which is depicted in Fig. 1 [1].

India

Three outbreaks of NiV have been reported in India since 2001. First outbreak was reported in Siliguri, West Bengal; between January and February, 2001. Total 66 cases and 45 deaths were

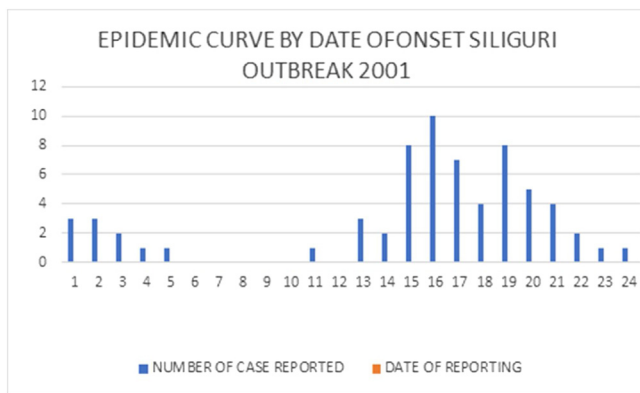


Fig. 2. Epidemic Curve by date of onset Siliguri, India outbreak 2001. Source: [27].

reported in this outbreak [20,23]. Second outbreak occurred in Nadia, West Bengal in 2007; 30 cases and 5 deaths were confirmed to be positive through real-time polymerase chain reaction (RT-PCR) as depicted in Fig. 2 [20,27]. Outbreak in Kerala, May 2018; reported 17 deaths with high case fatality. First index case was reported in Perambra, Kozhikode district. The outbreak began with three members of a family who died after cleaning an old well infected by bats.

Philippines

An outbreak of NiV or NiV like virus occurred in the southern part of Philippines affecting two villages of Mindanao in 2014. Horses were the source of infection and 17 cases were reported, seven of these were involved with either butchering activities or consuming horse meat and around 10 horses were reported to be dead [28].

Diagnosis

Laboratory diagnostic tests of NiV encephalitis consists of detecting anti-NiV immunoglobulin M (IgM) and IgG antibody in the serum and cerebrospinal fluid (CSF), with or without viral isolation. Most commonly used diagnostic method is enzyme-linked immunosorbent assay (ELISA) test, using monoclonal antibody-based antigen, for virus detection and for differentiating NiV from Hendra virus [1,6,19,20]. Direct ELISA test was used to detect anti-NiV-specific IgM, whereas, indirect IgG ELISA was used to detect the IgG antibody [6,29]. Other methods like serum neutralizing tests [6,30], RT-PCR for detection of viral RNA from serum, urine, and CSF [6,16,19,20,30], virus isolation [1,20,30] and nucleic acid amplification tests are available [1]. Magnetic resonance imaging (MRI) of the brain served as sensitive diagnostic tool in acute and relapse/late-onset NiV encephalitis, as the diagnostic sensitivity of ELISA was not reliable [6,20]. Different diagnostic techniques used globally are mentioned in Table 1.

Prevention

Preventive strategies can be incorporated to prevent NiV transmission. Patient to attendant transmission can be minimized through frequent hand washing and avoiding sharing of food and bed with patients. Wearing gloves and masks while handling of dead body is necessary to avoid corpse to human transmission. If this is not feasible in low and middle income countries at least thorough hand washing with soap and water immediately after the corpse contact may prevent disease transmission [13,31]. Nosocomial transmission to health care workers can be minimized by ensuring proper hand washing facilities, use of personal protective

equipment (PPE) and isolation of the meningoencephalitis patients during NiV outbreaks [13].

Measures like bamboo skirt method can be used to prevent the contamination of date palm sap. The method involves covering the shaved part and mouth of the pot by hanging a bamboo skirt. Other methods include sap branch method where the shaved part of the tree is covered with its own branches, cloth or mosquito net [12,32]. Washing or peeling of fruits and thorough hand washing while having fruits and preparing meals should be followed [33]. Strategies to improve awareness regarding risk factors and significance of adopting preventive measures can help in preventing the spread of infection [20]. Various communication strategies like local television or radio channels and print media were used to create awareness among people [12].

Vaccines

Studies have demonstrated that after challenging with NiV, ferrets and Syrian hamsters, vaccinated with recombinant vesicular stomatitis (rVSV) expressing NiV glycoproteins (attachment protein) and F(fusion) protein, showed complete protection against the lethal NiV infection, while animals in control group showed characteristic clinical signs of the disease [34,35]. Single dose rVSV vaccination has demonstrated to be effective when it was administered a day before the challenge. It has shown to be partially protective when administered at the early hours following the NiV infection in hamsters [36]. Single dose replication-defective vesicular stomatitis based-vaccine expressing NiV G and F proteins, also showed complete protection in the Syrian golden hamster model [37].

Effect of the vaccine, G glycoprotein of Hendra virus (HeVsG) has displayed that ferrets were protected from acute NiV disease for a duration of at least 12 months post vaccination [38].

Immunization of recombinant measles vaccine (rMV) along with the administration of the same amount of booster dose to both hamsters and monkeys revealed that, there was no clinical signs of the disease in both the animals and survived after challenging with NiV after 1 week of second immunization [39]. Monoclonal antibody (m102.4) against the G glycoprotein of the NiV, if administered pre-exposure or up to 10 h after exposure has shown to prevent the disease condition in ferrets [7,25].

Control

After identification of the virus in Malaysia outbreak, agricultural labourers were shifted from the place contaminated with NiV and suspected farms were closed [23]. More than a million pigs were culled and strict quarantine measures on pig movements were imposed [25]. Information regarding the virus was broadcasted through media [23]. Education about personal safety in case of contact with pigs and standard operating procedures were developed for people who were handling the dead bodies of NiV cases [23]. Information, education and communication in different languages was used to create awareness in the community [40]. Dissemination of information regarding NiV through official websites and hotline numbers were undertaken by the government [23]. Slaughterhouse workers and people involved in handling and management of pigs were suggested to use PPEs and proper hand-washing techniques [23]. All healthcare workers including relatives of infected persons were recommended to use PPE as they were more prone to develop infection [23]. A major control measure during this outbreak, was restricting import of live pigs through Malaysia [41].

There were more than five rural hospitals in Bangladesh, which reported maximum number of NiV cases. As mentioned in a commentary, there is a need for infectious disease control infrastructure in the hospitals. As repeated episodes of NiV outbreak were seen

in Bangladesh during harvesting season of date palm sap, the government emphasized on avoiding date palm sap or boiling it for at least ten minutes before consumption [12]. Stringent isolation procedures were followed at the treatment centers in Kerala, India, and measures to prevent droplet infection were initiated [16].

Treatment

A broad spectrum antibiotic, Ribavirin was the drug of choice in Malaysian outbreak for treating NiV encephalitis, leading to 36% reduction of mortality among humans [42]. Ribavirin also delayed the death of NiV infected hamsters by five days. Administration of chloroquine alone or combined with ribavirin did not provide any protection against NiV disease [43].

Favipiravir (T-705) demonstrated inhibition of NiV replication and transcription at the molecular concentration. In Syrian hamster model, administration of favipiravir orally twice daily or subcutaneously once daily for 14 days protected the animals [44]. Monoclonal antibody (m102.4) when administered to African green monkeys twice post exposure to NiV beginning on day 1, 3 or 5 and again after two days had shown to prevent the disease condition even after they developed clinical signs of the disease [45].

Supportive treatment remains the most common mode of treatment for acute Nipah encephalitis. Broad-spectrum antibiotic for nosocomial infections, prevention of deep venous thrombosis, mechanical ventilation and anticonvulsants for patients with seizures are some of the treatment measures given to infected patients [6].

Surveillance

Surveillance helped in analyzing the viral strains and monitoring the changes of viral factors. Cluster based surveillance helped to identify two types of Nipah outbreaks with high fatality rate, whereas case based surveillance identified sporadic NiV introductions in a study done in Bangladesh [46]. Another commentary on policy options for Bangladesh mentioned that early detection of outbreaks was achieved by setting up a surveillance system in five hospitals across the NiV belt [12]. A study done in Malaysia during 1999 outbreak conducted surveillance in human health sector, animal health sector and for reservoir hosts. Three categories were covered under human health sector such as disease surveillance, patient surveillance and high risk group surveillance [23]. Data regarding the roosting behavior of bats, their access to date palm sap and virus sequences among bats at different locations was collected to give evidence that environmental factors played an important role in NiV infection spread by Pteropus bats carrying the virus [47–49].

Economic burden

The NiV outbreak in Malaysia caused a tremendous economic loss because of the culling of over 1.1 million pigs to control the outbreak [4]. A case study done in Malaysia reported lowered standard of living mainly due to lack of opportunities to work in pig farms. Lack of employment opportunities led to out-migration of young labour force in affected areas which further contributed to the economic burden. Out of pocket expenditure did not contribute to economic burden as there was a robust public health system to support the patients. [50].

Strength & limitation

This narrative review summarizes the important scientific evidence available on NiV. Limitation of this literature review was language restriction of included articles to English.

Conclusion

Varied NiV disease pattern in Malaysia–Singapore and Indo–Bangladesh outbreaks was observed. In Malaysia and Singapore, NiV was transmitted from pig to humans whereas, in Bangladesh the cultural practices of consuming date palm sap contaminated by the infected bats, led to the repeated outbreaks. In India outbreak was observed in West Bengal region, sharing border with Bangladesh, due to spillover of virus from Bangladesh. The outbreak in Kerala, India started with direct contact of humans with bats and consequent nosocomial infection. The authors conclude, environmental factors play a vital role in the emergence of zoonotic disease in humans. Climatic changes due to factors like drought or floods, deforestation, urbanization, industrialization on large scale leads to destruction of animal habitats causing starvation and low immunity, increasing the viral load in their body, excreted in the secretions of bats, thereby infecting the fruits, animals or humans who come in contact with them. Hence, it is necessary to adopt ‘one health’ approach by considering human, animal and environmental health into the same context to address this particular disease. The NiV outbreaks in Malaysia and Singapore in 1999 ended with the mass culling of pigs and did not recur, whereas, multiple outbreaks have occurred in India and Bangladesh since 2001. The reasons for multiple outbreaks may be varied, nevertheless, low healthcare system capacity and lack of a robust surveillance strategy contribute substantially to it. Interdisciplinary and multi sectoral approach is vital in preventing the emergence of NiV. Along with these aspects it is necessary to undertake rigorous research for developing vaccines and medicines to prevent and treat NiV.

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Competing interests

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Ethical approval

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.jiph.2019.02.013>.

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