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Outbreaks of Varicella Zoster in a Military Nursing Institute: Infection Control in Hospital and Institutional Environments

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Abstract

Background: Varicella zoster (VZ) is a highly contagious exanthematous disease. The Indian VZ clade 5 has a high outbreak potential with attack rates of 90%, which thwarts all the infection control endeavors in hospital and institutional environments. Four VZ outbreaks occurring over four different years were investigated with military nursing students in a tertiary-care hospital in order to delineate infection control protocols.
Methods: VZ outbreaks were investigated by hospital infection control committee utilizing standard definitions and protocols after establishing epidemiological linkage. A total of 114 nursing students were evaluated through a questionnaire developed to assess clinicodemographic, exposure, confinement and vaccination parameters. Outbreak control measures included isolation of patients; quarantined close-contacts and suspects; acyclovir treatment; immunization of susceptible candidates against VZ.
Results: There were four different outbreaks comprising a total of 23 patients including five breakthrough patients with cumulative attack rate of 39%. Most patients had mild VZ. Most common sources were friends. Also, 25 students had no exposure to VZ or VZ vaccine, and were identified to be susceptible candidates and accordingly, were vaccinated.
Conclusions: Outbreaks of VZ are emerging in the developing countries due to inadequate immunization coverage, primary failure to seroconvert, or failure to mount immune response despite seroconversion, or secondary failure due to waning immunity. Outbreaks of VZ may have variable epidemiological dynamics and may not be controlled with standard infection-control programs. There is a need to augment existing capabilities for optimizing outbreak management in institutional settings.

Keywords: Outbreak, Varicella Zoster, Infection Control, Vaccination, Quarantine

1. Background

Varicella zoster (VZ) is a highly contagious systemic disease caused by varicella zoster virus (VZV) (Human herpes virus type 3) with humans as the only reservoir. VZ causes a self-limiting exanthematous disease in children followed by lifelong immunity. VZ causes a severe disease in adolescents, adults, neonates, infants, and critically ill and immunocompromised patients leading to bacterial superinfections such as pneumonia, bronchitis, encephalitis, meningitis, and musculoskeletal infections in approximately 20% of the cases. Deep-seated infections are associated with thrombocytopenia, bacteremia, persistent fever, intensive care, hospitalization, and mortality in 0.01% - 5.4% of hospitalized cases. Life threatening infections such as necrotizing fasciitis, pyomyositis and sepsis are known. Reported mortality is 1 in 60,000 patients totaling 7,000 deaths globally. Latency associated with VZV can result in herpes zoster, herpes ophthalmicus, zoster sine herpete, and post-herpetic neuralgia in 10% - 20% of the patients (1-3).

VZ clade 5 based in India has a high outbreak potential, which thwarts infection control endeavors in hospital and institutional environments. VZ in nursing staff can

spread to healthcare professionals (HCP) and susceptible patients through close contact, aerosol transmission, and conjunctiva as portals of entry. Since the attack rate is 65% - 87% in household settings, it is likely to reach 90% in hospitals and institutions. Outbreaks in critical areas of hospitals such as solid-organ and hematopoietic stem-cell transplant centers, oncology, burns, adult and neonatal intensive care units are difficult to control (4-7). The current study aimed at investigating repeated VZ outbreaks occurring over four years amongst military nursing students in a tertiary-care hospital in order to delineate infection control protocols.

2. Methods

All outbreaks of VZ involving military nursing students, healthcare staff, patients, and visitors were under surveillance of the hospital infection control committee after approval and written informed consent was obtained from the participants. VZ outbreaks were established on the criteria of > 5 patients related in time and place occurring within one incubation period of 10 - 21 days after the occurrence of VZ in the patient. However, > 5 patients in nursing institute was considered as the outbreak. Diagnosis in fresh patients was based on clinical definitions of an illness with acute onset of diffuse (generalized), maculopapular and vesicular rashes without other apparent manifestation. A patient concordant with clinical definition, but not laboratory confirmed or epidemiologically linked to a confirmed case was deemed a probable patient. Susceptible patients meeting clinical definitions were confirmed after establishment of epidemiological links during outbreak investigation without the requirement of laboratory confirmation of VZ as per extant guidelines by the centre for disease control (CDC), USA. Diagnosis of breakthrough patients was modified to accommodate VZ of shorter duration, few, and atypical lesions occurring after 42 days of vaccination (8, 9). Recovery from VZ infection was considered after an afebrile period of 48 hours and scabbing of VZ rashes. A total of 114 nursing students were evaluated through a guided questionnaire about clinicodemographic, exposure, confinement, and vaccination parameters. Source tracing was attempted. Outbreak control measures included isolation and confinement in hospital wards and hostels till crusting of lesions in fresh patients, and until no new lesion appeared in the patients. All close contacts and susceptible cases were quarantined in hostels. All confirmed patients were administered with 800 mg acyclovir five times a day along with symptomatic treatment. Presumptive evidence of immunity against VZ was collected from history of VZ or vaccination. Surveillance was continued through two full incubation periods comprising 42 days after the disease onset in last identified patient to ensure end of outbreaks (5).

3. Results

The military nursing institute had 114 female nurses aged 18 - 24 years spread over four academic years residing in shared rooms with a capacity of one to four students. The students also had close-contact during dining, library, classroom, hospital-training, and recreational activities. Their mean ± standard deviation (SD) age was 20.7 ± 1.42 years [95% confidence interval (CI): 20.6 - 20.8], with 77 students in the age range of 20 - 22 years.

There were four different outbreaks comprising ≥ 5 VZ patients each presenting in less than 42-day intervals, involving nursing students, healthcare staff, patients, and visitors. There were six, five, seven, and five patients in 2012, 2013 (two patients with breakthrough VZ), 2015, and 2016 (three patients with breakthrough VZ) respectively, comprising a total of 23 patients with the mean age of 20.52 ± 1.12 years (95% CI: 20.42 - 20.62). One patient encountered VZ in 2012 and 2013 in two consecutive outbreaks. Most patients had mild VZ with limited centripetally-distributed lesions. The five patients with breakthrough varicella had similar presentations compared with fresh patients; 12/23 (52.2%) were confined to hostel rooms due to unavailability of female isolation beds during outbreaks. No patients had progressive VZ with development of new lesions beyond seven days. Hospitalized patients were most commonly identified as first the patients during outbreaks. There were no herpes zoster or mortality related to VZ. The clinicodemographic and outbreak characteristics are tabulated in Table 1.

Totally, 32 (28.1%) students had VZ before joining the institute from 1995 to 2009 including one VZ occurring in the neonatal period; 33/114 (28.94%) were immunized, 16/33 (48.5%) by single-dose and 17/33 (51.5%) by double-dose vaccine. After single-dose immunization, two students encountered VZ once, and one student twice; 25 students had no exposure to VZ or VZ vaccine and were identified as susceptible candidates and offered double-dose and/or booster-dose VZ vaccine to control the infection.

4. Discussion

The current outbreak investigation for VZ occurring amongst military nursing students over four years was conducted to reach prevention and control initiatives in the healthcare environment. Occurrence of VZ outbreaks in young females in four consecutive years reveals the heterogeneous pattern of childhood exposures and protec-

Table 1. Clinicodemographic and Outbreak Characteristics in Varicella Zoster Outbreaks in 2012, 2013, 2015, and 2016

		Frequency, %	Age	SD	95% CI
Clinicodemographic Characteristics (n = 23)					
1	Mean age, y	20.5	-	1.12	20.4 - 20.6
2	Fresh patients	19	82.6	-	67.1 - 98.1
3	Breakthrough VZ	5	21.7	-	4.8 - 38.5
4	Lesions < 50 (mild VZ)	15	65.2	-	45.7 - 84.7
5	Lesions 51 - 250 (moderate VZ)	3	13	-	-
6	Lesions > 250 (severe VZ)	5	21.7	-	4.8 - 38.5
7	Average number of lesions	252.57	-	562.37	238.1 - 267
8	Pruritus	4	17.4	-	1.9 - 32.9
9	Fever	11	47.8	-	27.4 - 68.2
10	Weakness	6	26.1	-	8.1 - 44.1
11	Upper respiratory infection	1	4.3	-	-
12	Hospitalizations	10	43.5	-	23.2 - 63.8
13	Confined to hostel	12	52.2	-	31.8 - 72.6
14	Mean period of hospitalization (d)	8.9	-	3.75	8.12 - 9.68
15	Post-exposure immunoprophylaxis	1	4.3	-	-
16	Post-exposure chemoprophylaxis/chemotherapy	14	60.9	-	41 - 80.8
17	Duration of acyclovir therapy, d	6.1		4.39	5.14 - 7
Outbreak Characteristics (n = 23)					
1	Mean incubation period, d	9.05	-	1.1	8.3 - 9.8
2	Pooled attack rate (23/59)	39%	-	-	26.5 - 51.4
3	Mean VZ cases	1.92	-	1.1	1.5 - 2.4

tive titters. Close contact through accommodation, academic, and recreational activities facilitated transmission. The epidemic curve revealed rapid secondary attack occurring within a short period despite isolation and quarantine measures. There were 25 susceptible contacts within the cohort of 114 students. Breakthrough VZ was unpredictable.

Outbreaks of VZ are emerging in the middle and low income countries due to inadequate immunization coverage, primary failure to seroconvert after exposure to VZ or vaccine, failure to mount immune response despite seroconversion, or secondary failure due to waning immunity (2-6, 10). Outbreaks in hospitals and institutions can continue for long periods of six months due to huge footfall of patients/contacts/students/participants with VZ. Healthcare personnel (HCP) and other employees contracting VZ lead to sickness absenteeism attributable to VZ, which may range from seven to twenty days, even if the period of hospitalization is less. Outbreaks are reported in nurses more commonly than other HCP as they form the first contact with patients, attendants, and visitors and consequently may transmit VZ to more people (2, 5, 6). Though outbreak prevention measure through pre-emptive vaccination was adopted after four outbreaks in the institute, it was a step forward in a developing country due to prohibitive costs of VZ vaccine.

Isolated case-patients of VZ need to be investigated in hospital and institutional settings before the onset of possible outbreak. Diagnosis is clinical in most case-patients as VZ IgM is not reliable. Molecular tests are resource intensive, unsuitable for outbreaks and hence not recommended. IgM is suggestive of primary infection although it does not exclude re-infection or reactivation of latent VZV. Four-fold rising VZ IgG is specific, but not sensitive to VZ infection due to high titters in pre-exposed and vaccinated persons. Whole-cell IgG is not sensitive. Purified glycoprotein IgG, fluorescent antibody to membrane antigen (FAMA) IgG, and IgG avidity are not widely available commercially. Target amplification and genotyping are used to differentiate wild-type and Oka vaccine-strain VZV, in vaccine adverse-events (1, 2, 4).

Caveats to VZ transmission and infection control ex-

ist due to variable incubation period during which multiple co-circulating genotypes of VZ can be transmitted from multiple sources due to close contact with patients and other HCP (11). VZ transmissions cannot be effectively controlled by standard infection control practices such as hand-hygiene and avoiding handshake as nosocomial transmission of VZV from patients, visitors and HCP is well recognized through aerosols without the history of direct contact with index patient (2). Even the high-income countries with adequate vaccination coverage have instituted outbreak control and disease notification guidelines due to higher risk of associated complications (12).

Outbreaks of VZ may be controlled by post-exposure VZ vaccination within three days of exposure or acyclovir or valacyclovir chemoprophylaxis amongst susceptible exposed personnel from seven to ten days after exposure for seven days. No resistance is reported in VZV (13). Vaccination within three days of exposure is 90% effective compared with 70% within five days. Vaccination is effective even if the outbreak is identified late as it can cover people not yet exposed, thereby shortening the duration of the outbreak. Single-dose vaccinated individuals can be given a second-dose during outbreaks (1, 6, 12). Pre-exposure strategy of VZ vaccine immunoprophylaxis can confer long-term protection up to 20 years in 90% of vaccinees. Re-exposure to wild virus in single-dose VZ boosts immunity conferring the protection of vacinees against both VZ and herpes zoster, which ameliorates the need for booster vaccination.

VZ vaccine is contraindicated in patients who are critically ill, pregnant, with cancer of bone marrow or lymphatic system, on chemotherapy, or on transfusions in the past five months. The live-attenuated VZ vaccine in immunocompromised patients can be ineffective or deleterious, with reports of vaccine-related VZ in patients with T-cell defects. VZ vaccine can be given to HIV+ patients with good CD4 counts, X-linked agammaglobulinemia, common variable immunodeficiency, IgA, IgG subclass and complement deficiency, phagocytic and neutrophil disorders, and acute lymphocytic leukemia in remission. VZ vaccine also protects against oral and genital herpes infections. Risk of herpes zoster from Oka/Merck vaccine strain of VZ is significantly less than that of the wild VZ. A higher dose of VZ vaccine is available to protect against herpes zoster (1, 12).

Single-dose VZ vaccine has an efficacy of 94.4% compared with 98.3% with double-dose vaccine as a higher proportion of adults may not respond to the first dose. The global effectiveness for single- and double-dose VZ vaccines is 81% and 92%, respectively. Even single-dose vaccine has effectiveness of 100% against the severe disease (14). VZ double-dose vaccine is recommended for healthcare, military, school, college, humanitarian emergency, and correctional and institutionalized settings. Recommendations also exist for non-pregnant females of child bearing age, as well as adolescents and adults living with children and international travelers (1, 8, 9). Since its licensing in 1995, VZ vaccine has helped to achieve national goals of many nations through herd protection, outbreak control, reduced VZ-related hospitalizations, and direct and indirect costs. VZ vaccination is included in recommended vaccination schedules of many affluent countries worldwide as per the world health organization (WHO) recommendations of 80% vaccination coverage under herd immunization strategy. Epidemiological game-theory revealed that Nash-vaccination coverage by self-interest was lower compared with group-optimal utilitarian vaccination coverage, with the exception of VZ (15, 16). The availability of MMRV with measles, mumps, and rubella suits incorporation in universal immunization program, albeit even single-dose VZ vaccination remains prohibitively expensive on a large scale and only few countries fund the vaccine through national health systems (1, 15, 16). However, targeted vaccinations of HCP, transplant recipients and susceptible adolescents are proven cost-effective in high-income countries and likewise recommended by Indian Academy of Pediatrics (1, 5).

Persons at increased risk of severe VZ and in the ones where vaccine is contraindicated require VZ immune globulin (VZIG) prepared from plasma of healthy voluntary blood donors with high antibody titters to VZV, or zoster immune globulins (ZIG) prepared from patients recovering from herpes zoster, within 96 hours ensuing demanding costs. ZIG has lower attack rates amongst immunocompromised if administered within 96 hours of exposure. VZIG in exposed pregnant females without evidence of immunity is protective for mother rather than fetus. VZIG is recommended for neonates whose mothers get VZ peripartum, even if mother has received VZIG. VZIG is not recommended for full-term healthy infants exposed postnatally, even if there is no maternal history of VZ (1, 4).

VZ epidemiology in post-vaccine era consists of increasing age of infections due to primary immunization of younger population and decline in herpes zoster in immunized ones (1). Large VZ outbreaks in hospitals, daycare, schools, institutes, military, and cruise ships worldwide comprising single-dose immunized subjects are called for enhanced disease surveillance and control through acyclovir chemoprophylaxis or immunoprophylaxis amongst susceptible persons (5, 6, 8, 9, 17-21). Mathematical modeling based predictions also show the outbreak potential of both natural and breakthrough patients with single-dose vaccine, compared with sharp decrease in the incidence with double-dose vaccine (1). Double-dose vaccine, recom-

mended since 2006, decreased the intensity, number (50 skin vesicles compared with 200 - 400), size, and duration of outbreaks with effects 3.3-fold lower than that of double-dose vaccine. Nevertheless, breakthrough VZ may occur after infection by a wild-type virus in 7.2% - 15% single-dose vaccinees over a 10-year follow-up period, or few years after occurrence of VZ, or even after double-dose immunization, although the disease is subdued in intensity, duration, and presentation (2, 17).

Concurrent outbreaks of VZ, measles, and rubella are reported, which may confuse the clinical presentation requiring laboratory confirmation on VZV antigen through direct fluorescent antibody, anti-VZV IgM capture assay, four-fold rise in anti-VZV IgG, viral isolation, and molecular methods. Virus isolation and molecular methods can differentiate between wild-type and vaccine strains of VZV (12). Ongoing surveillance is required even with the best vaccination programs due to variations in vaccine coverage, efficiency, and waning immunity. Concurrent outbreaks can be an indicator of MMRV vaccine coverage and efficiency in target populations in future (8).

Institutional settings have a close-knit fraternity getting medical attention in designated hospitals, staying together in designated areas and children studying in specific schools. Electronic notification may be instituted in addition to paper-based notification under Group 'C' (7, 22, 23). The surveillance can be extended to evaluate susceptible candidates for VZ vaccine. A strategy for surveillance and vaccination is hereby proposed for independent institutional set ups in Table 2. Post-vaccination serosurveillance of anti-VZ antibodies can be done by simple latex agglutination, which can detect antibodies up to 11 years and is more sensitive than the enzyme-linked immunosorbent assay (ELISA). The community should also be exposed to health education programs in schools and community centers during high-attendance events such as parents-teacher meetings, ladies meeting, and cultural programs (24, 25). Monitoring can be done electronically through Delphi techniques and creation of text-based communication systems for clientele feedback, early reporting and passive surveillance (2, 26, 27). Mandatory double-dose VZ vaccination for healthcare staff on induction, and immunocompromised population along with their susceptible household contacts go a long way towards infection and outbreak control, ensuring the safety of providers and patients against VZ. Static modeling and surveillance systems can be employed to evaluate targeted vaccination programs as well as unimmunized population. VZ and herpes zoster are eradicable if the vaccine is universally accessible and acceptable (28).

4.1. Conclusions

The management of patients and susceptible cases by isolation, confinement, quarantine, chemoprophylaxis, and immunoprophylaxis represents immediate and long-term response measures against VZ outbreaks. Outbreaks of VZ may have variable epidemiological dynamics and may not be controlled with standard infection control programs. Institutions with a close-knit fraternity need to augment the existing capabilities through pre-emptive double-dose and/or booster-dose VZ vaccination to optimize the outbreak management and control.

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Footnotes

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Table 2. Model Varicella Zoster Surveillance and Control Algorithm for Institutional Settings

S. No.	Event/Susceptible Population	Pre-Exposure Surveillance and Control	Vaccination	Organizational Responsibility	Post-Exposure Surveillance and Control	Immuno/Chemoprophylaxis	Organizational Responsibility
Post-Outbreak Algorithm							
1.	Hospital outbreaks	-	-	-	Outbreak investigation	Double-dose to all high risk susceptible cases	Sponsored mandatory immune-chemoprophylaxis/treatment
					Notification	Oral acyclovir/valacyclovir	
2.	Outbreaks in residential pockets including military camps	-	-	-	Outbreak investigation	Double-dose to all high risk susceptible cases	Sponsored chemoprophylaxis/ treatment
					Notification	Oral acyclovir/acyclovir	
3.	Institutional outbreaks (military/academic/religious/cultural institutes)	-	-	-	Outbreak investigation	Double-dose to all high risk susceptible cases	Sponsored mandatory immuno/chemoprophylaxis/ treatment
					Notification	Oral acyclovir/valacyclovir	Self-financed vaccination
Comprehensive Algorithm							
1.	Healthcare professionals (personnel with positive disease history may be susceptible)	Pre-induction screening	Double/booster dose	Sponsored mandatory vaccination	Disease or vaccination history	Double/booster dose VZ vaccine	Sponsored mandatory immuno/chemoprophylaxis/ treatment
		Disease or vaccination history			Home isolation and confinement	Oral acyclovir/valacyclovir	
		Serology test for anti-VZ antibodies			Daily screen of fever, lesions, and systemic symptoms by ICN		
2.	Immunocompromised patients (including HIV+ with CD4 count > 200/μL)	Serology test for anti-VZ antibodies	Double/booster dose	Sponsored mandatory vaccination	Institutionalized isolation	Oral acyclovir/valacyclovir	Sponsored mandatory chemoprophylaxis/treatment
					Daily screen of fever, lesions, and systemic symptoms by ICN		
3.	Susceptible household contacts of immunocompromised	Disease or vaccination history	Double/booster dose	Sponsored mandatory vaccination	Home isolation and confinement	Oral acyclovir/valacyclovir	Sponsored mandatory chemoprophylaxis/ treatment
4.	Non-pregnant females of childbearing age	Serology test for anti-VZ antibodies	Double/booster dose	Parent education	Disease or vaccination history	Oral acyclovir/valacyclovir (pregnancy to be avoided for treatment	Sponsored mandatory chemoprophylaxis/ treatment
				Self-financed	Home isolation and confinement		
					Selective institutionalized isolation		
5.	Pregnant females	Disease or vaccination history	Double/booster dose on completion or termination of pregnancy	-	Institutionalized isolation	Varicella zoster immune globulin or zoster immune globulin	Sponsored immunoprophylaxis

6.	Neonates/infants	History of maternal vaccination	VZ vaccine or MMRV for increased coverage	Parent education	Institutionalized isolation	Acyclovir/valacyclovir	Sponsored mandatory chemoprophylaxis/ treatment
		Disease history during pregnancy		Self-financed	Daily screen of fever, lesions, and systemic symptoms by ICN		
7.	Patients/visitors reporting to hospitals	Disease or vaccination history	Double/booster dose	Patient education	Home isolation and confinement	Oral acyclovir/valacyclovir	Sponsored mandatory chemoprophylaxis/ treatment
				Self-financed	Selective institutionalized isolation		
8.	Military inductees/recruits/susceptible personnel And students in schools and colleges	Disease or vaccination history	Double/booster dose	Parent and teacher education	Home isolation and confinement	Oral acyclovir/ valacyclovir	Sponsored mandatory chemoprophylaxis/ treatment
				Self-financed	Selective institutionalized isolation		
				Opening vaccination kiosks in schools			
9.	Vaccinees with Varicella like rash	-	-	-	Daily monitoring of rash	Continue second dose	Patient education
					Avoidance of contact till crusting/fading away of rashes		
					No new lesions in 24 h		