CLINICO-RADIOLOGICAL PROFILE, POLYMERASE CHAIN REACTION (PCR)- POSITIVITY AND OUTCOME - ANALYSIS IN HOSPITALIZED SUSPECTED H1N1 PNEUMONIA; EFFICIENCY ASSESSMENT OF HEALTH CARE DELIVERY SYSTEM. A PILOT STUDY

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ABSTRACT

Background: H1N1 pneumonia has been posing a serious public health challenge globally since 2009. The pneumonia is a serious disease, not only difficult to diagnose but also commonly leads to a fatal outcome.

Aims and Objectives: The main objective was to determine possible factors predicting PCR-positivity and a fatal outcome. Another aim was to assess the efficacy of healthcare delivery system.

Material and Methods: This was a prospective, descriptive study conducted at the Lady Reading Hospital, Peshawar, from October 2015 to February 2016. The data was collected and recorded on a preset, structured data-collection form.

Results: Out of the total 145 suspected cases, 37 were selected for the study. The baseline characteristics studied were age, gender, pregnancy status, urban/rural residence, symptoms and signs, time to admission, radiological findings, oxygen saturation, need for ventilatory support, PCR-positivity and non-fatal/fatal outcome. The overall PCR-positivity and fatality was 11 (29.7%) and 14 (37.8%) respectively. The only factor which could predict a positive PCR and was statistically significant, was bilateral mid and lower zone consolidation on CXR, 10 out of 26 (38.5%) cases as compared to 01 out of 11 (9.1%) cases among other CXR findings (P= 0.00023). The factors associated with high fatality were hypoxia (oxygen saturation <80%) and the need for invasive ventilation, each associated with 09 out of 15 (60%) fatalities (P= 0.0217) and 14 out of 15 (93.3%) fatalities (P= 0.0007) respectively. No patient was previously flu-vaccinated. Majority (56.8%) of the patients were admitted after 5 days of symptom onset. PCR-diagnostic facility was provided to 25.5% of the suspected cases. Ventilatory support was provided to less than half (46.7%) of the total cases needing invasive ventilation. Oseltamivir treatment (both free and self-sponsored) was provided to only 59.5% cases.

Conclusion: Proper patient selection can yield a greater PCR-positive case-detection in H1N1 pneumonia as it is a serious disease with high mortality, improvement needs to be brought at all levels for prevention and early diagnosis to timely treatment.

Key Words: H1N1 Pneumonia; Presentation; Diagnosis; Management

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INTRODUCTION

Influenza has been recognized as one of the oldest respiratory disease of mankind. Its history dates back to over 2000 years.[1] Influenza, an upper respiratory tract infection caused by RNA viruses of the family Orthomyxoviridae, can affect birds (Avian) and mammals (Human).[2] Any strain of influenza virus that is endemic in pigs is called swine-origin influenza virus.[3] influenza viruses type A, B and rarely C are

responsible for human disease throughout the world.[4]

The virus responsible for 2009 influenza pandemic emerged from a novel combination of genes from human, swine and Eurasian avian viruses[5] and was first reported from Mexico.[6] The virus possibly originated from triple re-assortment of swine viruses circulating in Pigs since 1997-98.[5,7]

The virus causing 2009 pandemic of H1N1 is now a regular human flu virus and continues to circulate seasonally world-wide and in the sub-continent.[8-11] Although cases of H1N1 infection have early symptoms similar to seasonal influenza but they frequently progress to pneumonia, respiratory failure and multi-organ failure resulting in death. Reliable confirmatory test, like real-time reverse transcriptase-polymerase chain reaction (rRT-PCR), became available quite early but is not usually accessible during the outbreaks. The clinico-radiological judgment of attending physicians may become important in directing timely antiviral therapy to get favorable outcome. This highlights the necessity to determine the clinico-radiological predictors for diagnosis of H1N1 infection. The non-specific presentation of H1N1 infection makes it difficult to distinguish clinically from other respiratory infections. A study describing clinico-radiological finding in PCR-confirmed H1N1 infection was published from India in May 2015.[11]

At the beginning of the winter season, severe pneumonias were noted in patients form different areas of the Khyber Pakhtoonkhwa province. A striking similarity of symptoms (preceding flue-like illness) and severity (hypoxia and respiratory failure) were noted. Bilateral mid and lower zone involvement on chest X-Ray (CXR) and poor response to antibiotics raised the possibility of a viral pneumonia. In the mean time, occasional reports of H1N1 pdm 09-positive flu in Pakistan appeared in the media. Non-availability of specific nasopharengeal/throat swabs, viral transport medium (VTM), diagnostic PCR and drug (oseltamivir) in government sector hospitals was a problem. This prompted us to develop Liaison with the National Institute of health (NIH) through provincial Director General of Health (DGH) office for free provision of diagnostic PCR and drug (oseltamivir) facilities. Efforts were also made for the availability of oseltamivir in the private sector. A pilot-study was also designed to outline the demographic and clinico-radiological profile of clinically suspected H1N1 pneumonia. The aim was to determine possible factors predicting rRT-PCR positivity and a fatal outcome; as well as to assess the efficiency of healthcare delivery system. This could help us tackle such outbreaks more efficiently in the future.

MATERIAL AND METHODS

Study Design, Setting and Population

This was a prospective, descriptive, study conducted in the department of Pulmonology, Lady Reading Hospital, Peshawar. It's a tertiary care teaching hospital. A total of 145 cases suspected of H1N1 pneumonia presented to the hospital over a period of 04 months from October 2015 to February 2016. Out of these, 37 patients were selected, applying non-probability consecutive- sampling technique. The inclusion criteria were age more than 14 years, severe pneumonia (CRB-65 > 2), preceding-flu and/or bilateral infiltrates on CXR and free of cost provision of VTM and diagnostic PCR facilities.

CASE DEFINITIONS

Pneumonia: was defined as acute respiratory symptoms with parenchymal infiltrates on chest X-Ray.

Suspected case of H1N1 infection: Was defined as a person with an acute febrile respiratory illness and bilateral clinico-radiological sever pneumonia.

Confirmed cases of H1N1 Pneumonia: Was defined as a person with an acute febrile respiratory illness, bilateral clinico-radiological sever pneumonia and laboratory confirmation of influenza A (H1N1) virus infection by rRT-PCR.

Indication for Invasive Ventilation

1). Oxygen saturation below 80% despite 01 hour of high flow (10 L/m) oxygen inhalation.

2). High flow (10 L/m) oxygen inhalation needed for more than 04 hours to keep oxygen saturation above 80%.

DATA COLLECTION

The data collection was done, at the time of sample collection for diagnostic PCR, after informed consent by the patients or their parents/guardians. This included demographic and clinico-radiological data. Data regarding oseltamivir-treatment, need for ventilation, rRT-PCR result and outcome (non-fatal/fatal) was recorded later as it became available. The data was recorded on a pre-set, structured data-collection form.

Sample collection; Storage and Transport:

Swab-kit, VTM, transportation facilities were provided by the NIH, Islamabad. Throat swab was collected from all the patients. Nasopharyngeal swab was also taken, using the same kit, form patients consenting for it. The sample was stored in a refrigerator till it was

transported in VTM to the regional centre in Peshawar and then to the NIH, Islamabad. The average temperature of refrigerator was 2 to 8ºC and the time range of refrigerated-storage before dispatch was 08 to 14 days.

STATISTICAL ANALYSIS

All the data was analyzed using the Statistical Package for Social Sciences version 16.0 (SPSS Inc., Chicago, IL, USA). Student's test was used for comparison of continuous variables; while Fisher's exact test was used for comparison of dichotomous variables. A p-value less than 0.05 was considered to be statistically significant.

RESULTS

Baseline demographic clinico-radiological characteristics, need for invasive ventilatory support, rRT-PCR results and non-fatal/fatal outcome of patients were recorded (Table 1). A total of 37 patients included 12 (32.43%) males and 25 (67.57%) females. 04 (10.81%) patients were twenty years or below and 33 (89.18%) were above twenty years of age. Two-third, 25 (67.5%), patients were rural dwellers. Five out of twenty five female patients, (20%), were pregnant. Common symptoms and signs included fever, cough, sore throat, nasal symptoms, chest pain, dyspnoea, wheeze and crackles. Time from symptom-onset to admission was variable. 02 (5.4%), 14 (37.8%) and 21 (56.7%) patients got admitted with in 02, 03 to 05 and after 05 days of onset of symptoms, respectively. The commonest CXR finding was bilateral mid and lower zone consolidation, 26 (70.3%) and others (broncho-pneumonia, ground glass and patchy infiltrates) accounted for 11 (29.7%). Only 04 (10.82%) had oxygen saturation above 90%, while 18 (48.64%) and 15 (40.54%) had between 80 to 90% and below 80% oxygen saturation on room air, respectively. Invasive ventilation was needed for 15 (40.5% of the total patients) but could only be provided to 07 (46.7%), less than half of the patients needing ventilatory support. Out of the 37 patients tested for H1N1 infection 11 (29.7%) were rRT-PCR positive. Moreover 14(37.8%) out of 37 patients had a fatal outcome.

Baseline characteristics as possible determinants of positive rRT-PCR, in suspected H1N1 infected patients, were studied (Table 02). 05 out of 12 (41.7%) male and 06 out of 25 (24.0%) female patients were PCR-positive (P=0.271). 02 out of 04 (50.0%) and 09 out of 33 (27.3%) were PCR-positive in the age group 20 years or below and above 20 years, respectively (P=0.589). 02 out of 05 (40.0%) pregnant and 04 out of 20 (20.0%) non-pregnant females were PCR-positive (P=0.348). Patients admitting to the hospital within 05 days and after 05 of onset of symptoms were 03 out of 11 (27.3%) and 08 out of 26 (30.8%) PCR-positive, respectively. Patients with symptoms of fever and cough, upper respiratory tract infection (URTI) and lower respiratory tract infection (LRTI) were PCR-positive, 11 out of 37 (29.7%), 09 out of 34 (26.9%) and 10 out of 37 (27.0%) cases, respectively. PCR was positive in significantly more patients with CXR finding of bilateral mid and lower zone consolidation as compared to other CXR findings, 10 out of 26 (38.5%) and 01 out of 11 (9.1%), respectively (P=0.00023). Oxygen saturation (on room air at the time of presentation), less than 80% and $\geqslant$ 80%, was associated with PCR-positivity of 05 out of 15 (33.4%) and 06 out of 22 (27.3%), respectively (P=0.692); and same were the figures for patients requiring vs not requiring invasive ventilation.

Baseline characteristics of patients were also analyzed as possible determinants of a fatal outcome (Table 03). Fatal outcome was observed in 04 out of 12 (33.3%) males and 10 out of 25 (25%) females (P=0.695). Fatal outcome in patients with age 20 years or less was 01 out of 4 (25%), a 19 years old pregnant lady, while 13 out of 33 (39.4%) patients above 20 years of age met a fatal outcome (P=0.575). 03 out of 5(60.0%) pregnant and 07 out of 20 (35.0%) non-pregnant, (P=0.307), had a fatal outcome. Fever and cough, URTI symptoms and LRTI symptoms were associated with a fatal outcome in 14 out of 37 (37.8%), 14 out of 34 (41.2%) and 14 out of 37(37.8%) cases, respectively. Time from symptom-onset to admission had no statistically significant effect on fatality, 06 out of 16 (37.5%) and 08 out of 21 (38.1%) for patients admitting within 05 days and after 05 days of symptoms onset, respectively (P=0.942). Bilateral mid and lower zone consolidation on CXR and other CXR findings were associated with fatality in 10 out of 26(38.5%) and 04 out of 11 (36.4%) cases respectively (P=0.904). Lower oxygen saturation was associated with significantly higher fatality, 09 out of 15(60.0%) and 05 out of 22 (22.7%) for less than 80% and for >80% oxygen saturation, respectively (P=0.021). The need for invasive ventilation was also associated with significantly higher fatality 14 out of 15 (93.3%) as compared to 06 out 22 (27.3%) fatalities in patients not requiring ventilatory support (P=0.000075). The only survivor among patients requiring artificial ventilation was among the patients who were provided ventilatory support.

Assessment of overall efficiency of healthcare delivery system to tackle H1N1 pneumonia was done, using various parameters (Table 04). Time to admission from symptoms onset, in the 37 study cases, was within 05 days in 16 (43.2%) and after 05 days in 21 (56.8%) cases. Out of 145 clinically suspected H1N1

Table 01. Baseline characteristics PCR-result and outcome of study cases (N=37)

Characteristics	No. (%)	Total cases (%)
Age		
15-20 years 21 – 39 years ≥ 40 years	04 (10.81) 14 (37.83) 19 (51.36)	37 (100)
Gender		
Male Female	12 (32.43) 25 (67.57)	37 (100)
Pregnan cy status		
Pregnant Non - Pregnant	05 (20.0) 20 (80.0)	25 (100)
Residence		
Urban Rural	12 (32.4) 25 (67.5)	37 (100)
Symptoms and Signs		
Fever Cough URTS (Sore throat, nasal symptoms) Haemoptysis Chest Pain Dyspnea and tachypnea Wheeze and crackles	37 (10 0.0) 37 (100.0) 34 (91.9) 06 (16.2) 35 (94.6) 34 (91.9) 30 (81.0)	37 (100)
Time from symptoms -onset to admission		
? 02 days 03 to 05 days 06 to 10 days 11 to 14 days	02 (5.4) 14 (37.8) 13 (35.1) 08 (21.6)	37 (100)
Radiographic Findings		
Bilateral mild and lower zone consolidation Others (Ground glass or pitchy infiltrates)	26 (70.3) 11 (29.7)	37 (100)
Oxygen Satur ation (on RA)		
>90% 80 – 90% < 80%	04 (10.82) 18 (48.64) 15 (40.54)	37 (100)
Invasive Ventilatory Support		
Needed Provided	15 (40.5) 07 (46.7)	22 (100)
PCR Findings		
PCR Positive PCR Negative	11 (29.7) 26 (70.3)	37 (100)
Outcome		
Non - Fatal Fatal	14 (37.8) 23 (62.2)	37 (100)

Table 2. Baseline characteristics as determinants of positive rRT-PCR

Characteristics	Positive PCR/ total PCR done (%)			P-value
Age	<20 yrs	>20 yrs		
	02/04 (50.0%)	09/33 (27.3%)		0.58901
Gender	Male	Female		
	05/12 (41.7%)	06/25 (24.0%)		0.347
Pregnancy status	Pregnant	Non-pregnant		
	02/05 (40%)	04/20 (20%)		0.348972
Symptoms	Fever & cough	URTI symptoms*	LRTI symptoms**	
	11/37 (29.7%)	09/34 (26.9%)	10/37 (27.0%)	
Time from symptoms onset to admission	≤5 days	>5 days		
	03/11 (27.3%)	08/26 (30.8%)		0.831573
Radiographic Findings	Bilateral mid & lower zone consolidation	Other CXR findings		
	10/26 (38.5%)	01/11 (9.1%)		0.000232
Oxygen saturation on room air	<80%	≥80%		
	05/15 (33.4%)	06/22 (27.3%)		0.692108
Invasive ventilation	Required	Not required		
	05/15 (33.4%)	06/22 (27.3%)		0.692108

*URTI: Upper Respiratory Tract Infection (Sore throat and nasal symptoms)
**LRTI: Lower Respiratory Infection (Dyspnoea, chest pain, heamoptysis, wheeze and crackles)

Pneumonia cases only 37 (25.5%) could be provided free of cost access to rRT-PCR diagnosis. In none of 37 cases, sample could be dispatched for rRT-PCR diagnosis within 07 days of collection. In all cases it took between 08 to 14 days to dispatch samples to regional centre of NIH. Out of 15 patients, needing invasive ventilation, only 07 (46.7%) could be ventilated because of limited availability of ventilators. Only 10 (45.5%) out 22 oseltamivir-treated patients were given free of cost oseltamivir. Fifteen (40.5%) patients could not be treated with oseltamivir because there was no free drug available and they could not arrange the drug by themselves. Moreover, none of the 37 cases was flu-vaccinated.

DISCUSSION

Seasonal influenza in South-Asia usually starts pre-winter and ends as summer sets in i.e. September to March[4] and mainly affects the elderly. H1N1 infection, as opposed to seasonal influenza, equally affects the young and the elderly.[5]

Our data suggests that most of the patients, both suspected and confirmed, belonged to young and middle age groups. Age –group of patients with H1N1 pneumonia worldwide is variable. This varied presentation may be due to the absence of any age-related predisposing factor. On the other hand, it has been suggested that patients above 60 years of age may be immune to H1N1 virus due to previous infection with influenza virus having similar antigenic structure.[12-16]

Most patients in this study were females in suspected and males in confirmed cases. This gender distribution is similar to other studies reporting either equal or male/female predominance.[10,11,17] The female predominance reported in some studies could be because of cultural differences. In some regions people traditionally go for more children, ten or more in some cases.

Table 03. Baseline characteristics as determinants of fatal outcome

Characteristics	Fatal outcomes/total outcomes (%)			P-value
Age	d 20 yrs	> 20 yrs		
	01/04 (25.0%)	13/33 (39.4%)		0.575082
Gender	Male	Female		
	04/12 (33.3%)	10/25 (40%)		0.695487
Pregnancy status	pregnant	Non pregnant		
	03/05 (60.0%)	07/20 (35.0%)		0.307434
Symptoms	Fever & cough	URTI symptoms	LRTI symptoms	
	14/37 (37.8%)	14/34 (41.2%)	14/37 (37.8%)	
Time from symptom onset to admission	⩽5 days	>5 days		
	06/16 (37.5%)	08/21 (38.1%)		0.942842
Radiographic Findings	Bilateral mid & lower zone consolidation	Other CXR findings		
	10/26 (38.5%)	04/11 (36.4%)		0.904273
Oxygen saturation on room air	<80%	⩾80%		
	09/15 (60.0%)	05/22 (22.7%)		0.021722
Invasive ventilation	Required	Not required		
	14/15 (93.3%)	06/22 (27.3%)		0.000075

Mothers, in such cases, may be less healthy and have weaker immunity because of extra-burden of multiple pregnancies. This could lead to more frequent progression of H1N1 flu to severe pneumonia.

Pregnancy in our case series was present in 20% of the female patients suspected of H1N1 pneumonia. More gravid females were PCR-positive as compared to non-gravid females, though not statistically significant, pregnancy does not predispose to increased risk of acquiring H1N1 infection, though it increases risk for developing H1N1 pneumonia in addition to increased morbidity and mortality.[18-20] It is due to the physiologic changes occurring during pregnancy that there is a high risk for complication of H1N1 infection in such patients.[21,22] The third trimester of pregnancy is associated with a significant fall in oncotic pressure. Therefore, H1N1 infection during pregnancy can rapidly lead to haemodynamic imbalance, worsening lung function, pneumonia, acute pulmonary oedema and respiratory failure.[23,24] Moreover, pregnancy reduces the ability to tolerate hypoxia thus increasing the risk for mortality.

The majority of our study cases belonged to rural population while the reverse was reported by an Indian study.[10] This could be because of the difference in the grouping of study-population of the two studies. Suburbs were grouped with 'Urban-group' in the Indian study and with 'Rural-group' in our study. Rural population, having less earning opportunities, could have weaker health and immune system and thus more frequent progression form H1N1 flu to Pneumonia.

The common clinical presentation in our study cases was with URTI, cough, fever and pneumonia, similar to those from other countries.[10,25,26] The commonest radiological abnormality in our study was bilateral mid and lower zone consolidation (70.3%) and was also reported form Oman and India,[11,27] as opposed to another Indian study reporting ground glass capacities in the majority (69%) of cases.[28] Both ground-glass opacities and consolidation have been reported to be the commonest radiological presentations by Ajlan et al.[29] They also observed progression of ground-glass opacities to multifocal areas of consolidation, in most cases, on serial radiographic studies.

Table 04. Determinants of efficiency of healthcare delivery system

Determinants	Yes	No	Total
Time to admission from symptom onsets onsets(⩽ 5 days)	16 (43.2%)	21 (56.8%)	37 (100%)
Free of cost access to rRT-PCR diagnosis	37 (25.5%)	108 (74.5%)	145 (100%)
Time to dispatch sample for PCR study after collection (⩽ 7 days)	0	37 (100.0)	37 (100.0%)
Access to invasive ventilation, if needed	07 (46.7%)	08 (53.3%)	15 (100.0%)
Oseltamivir treatment provided	22 (59.5%)	15 (40.5 %)	37 (100.0%)
Free of cost oseltamivir provided	10 (45.5%)	12(54.5%)	22 (100.0%)
Previous flu-vaccination	0	37 (100%)	37 (100.0%)

Two Korean studies also reported bilateral abnormalities and ground-glass opacities to be the commonest radiological findings.[30,31] Thus bilateral clinico-radiological pneumonia, in a patient with preceding flue, seems to suggest H1N1 virus infection. While pure symptoms-based screening tools helped to control SARS outbreak in 2003,[30] they failed to accurately predict H1N1 infection.[32]

The PCR positivity in our data, was 11 (29.7%) out of 37 suspected cases. This is higher than the overall national figure of 21% PCR positivity for Pakistan, reported by NIH, Islamabad.[8] Others studies have reported a PCR positivity of 23.0% (India), 23.5% (Canada),[32] 43.7% (Korea)[33] and 58.8% (Oman).[22,27] Our PCR positivity rate was better than some of the rates reported in other studies despite certain limitations, like delay in admission and sample-collection for PCR study as well as improper-storage and delayed-dispatch of samples for viral studies. This might be a reflection of better clinical case selection; and PCR positivity might be further increased by overall improvement of diagnostic services.

The only statistically significant factor associated with PCR positivity in our study was bilateral mid and lower zone consolidation of CXR (P=0.00023). Others have reported bilateral ground glass opacities followed by consolidation as common CXR indicator of PCR-positivity. As described earlier, symptom-based screening tools proved successful in predicting SARS outbreak[34] but failed to predict H1N1 infection.[32,35] On the other hand, relying solely on PCR-positivity consistently leads to under-estimation of case detection and transmission for H1N1 infection.[24] Forty-two percent of infected cases are estimated to be PCR-negative,[36] which is of significant public health importance. This may be caused by problems encountered with taking the swabs[12] and swabbing individuals in the late stages of the infections.[37] Early peaking of the viral load, with in two-days, leaves a narrow window of opportunity for diagnostic-PCR-positivity and for anti-viral treatment.[38,39]

The high (37.8 %) mortality associated with H1N1 pneumonia in our study indicates the seriousness of the pneumonia. Similar high mortality has been reported by two studies from India (56.3 %)[11] and (45.6 %),[10] while lower mortality is reported from Korea (13.5 %)[30] and Oman (16.4 %).[27] The difference in mortality rate could be because of the difference in the promptness and quality of medical care provided. This highlights the importance of early diagnosis and treatment including antiviral drugs and ventilatory support.

The factors responsible for statistically significant increased risk of mortality in our study were hypoxia (oxygen saturation <80%, P=0.021) and need for invasive ventilation (P < 0.0001). Pregnancy, though not statistically significant, also seems to be an important risk factor for mortality. Studies from around the world have reported older age,[40-42] pregnancy,[34] bilateral multi-zone pneumonia,[31] delay in hospitalization and anti-viral treatment-initiation[31] and need for invasive ventilation[33] as important determinants of mortality in H1N1 pneumonia.

The overall efficiency of health care delivery system was judged by various factors in an attempt to identify its deficiencies, so that future H1N1 outbreaks can be tackled more effectively. Less than half of the study patients were admitted to the hospital within five days of symptom onset, while only 5.4% were admitted within 48 hours of symptom onset when anti-viral treatment is maximally effective. Free access to diagnostic PCR and oseltamivir treatment was provided to a limited number of patients. The availability of diagnostic and therapeutic facilities for H1N1 infection in private sector is limited and expansive, usually beyond the reach of common man. Sample storage was done in the refrigerator as opposed to the recommended storage. Samples kept for more than 02 days need to be stored at -70°C. No sample

collected could be dispatched for PCR-study within 7 days. Ventilatory support whenever needed could not always be provided because of lack of enough ventilators. None of the patients had a prior flu-vaccination done. This demands us, as health professionals, to focus more on prevention and to be proactive rather than reactive.

CONCLUSION

High index of clinical suspicion and proper patient selection can yield a grater PCR-positive case-detection in H1N1 pneumonia. As it is a serious disease with high mortality, improvement in health care delivery system is needed to reduce mortality. Improvement needs to be brought at all levels from prevention, early admission and diagnosis to timely treatment. Treatment includes both specific antiviral drugs and specialized supportive-treatment like artificial ventilation. This could help reduce the high mortality associated with H1N1 pneumonia.

RECOMMENDATION

- Provision of flu vaccines (efficacy of 60%)
- Provision of free diagnostic kits
- Provision of free/subsidised antiviral drugs
- Provision of enough ventilatory support facilities
- Provision of isolation wards to check spread of infection
- Provision of regional diagnostic centres for timely diagnosis and treatment.

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