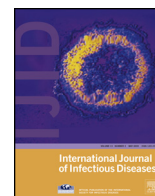




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Community Case Clusters of Middle East Respiratory Syndrome Coronavirus in Hafr Al-Batin, Kingdom of Saudi Arabia: A Descriptive Genomic study

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SUMMARY

The Middle East respiratory syndrome coronavirus (MERS-CoV) was first described in September 2012 and had caused a total of 191 cases of MERS-CoV infection with 82 deaths. Camels have been implicated as the reservoir of MERS-CoV, but the exact source and mode of transmission for most patients remain unknown. During a 3 month period, June to August 2013, there were 12 positive MERS-CoV cases reported from the Hafr Al-Batin district in the north east region of the Kingdom of Saudi Arabia. In addition to the different regional camel festivals in neighboring countries, Hafr Al-Batin has the biggest camel market in the entire Kingdom and host an annual camel festival. Thus, we conducted a detailed epidemiological, clinical and genomic study to ascertain common exposure and transmission patterns of all cases of MERS-CoV reported from Hafr Al-Batin. The genetic data indicated that at least two of the infected contacts could not have been directly infected from the index patient and alternate source should be considered. Camels appear as the likely source but other animals have not been ruled out. More detailed case control studies with detailed case histories, epidemiological information and genomic analysis are being conducted to delineate the missing pieces in the transmission dynamics of MERS-CoV outbreak.

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1. Introduction

Since the Middle East respiratory syndrome coronavirus (MERS-CoV) was first described in September 2012,¹ there have been a total of 191 cases of MERS-CoV infection with 82 deaths (43% mortality rate) reported to the WHO.² All cases have had links to the Middle East and the majority of cases (156 with 63 deaths (40% mortality) have been reported from KSA as of March 15, 2014. We previously reported family³ and healthcare associated⁴ case

clusters of MERS-CoV infections where human-to-human transmission occurred between index cases and their contacts. Whilst camels have been implicated as the reservoir of MERS-CoV,^{5–7} the exact source(s) and mode of transmission for most patients remain unknown. Serology consistent with a common MERS-CoV like virus in camels has been demonstrated by several studies^{5–7} and recently evidence has emerged of a MERS-CoV infection in a camel and in humans in contact with these camels.⁸

During a 3 month period, June 30, 2013 to August 31, 2013, there were 12 positive MERS-CoV cases reported from the Hafr Al-Batin district in the north east region of the Kingdom of Saudi Arabia (KSA). Hafr Al-Batin has the biggest camel market in the entire Kingdom with 500,000 camels being reared there. Hafr Al-Batin annually host drovers of more than 100 camel herds, comprising around 10,000 camels, from various regions of KSA,

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Kuwait, Qatar and the United Arab Emirates. This annual festival is known locally as “Mazayin al-Ibl, meaning “The Best of the Herds,” and attracts more than 160,000 people⁹ from November– December to March each year. This festival was the first to be established in the region and subsequently other camel festivals were started in neighboring countries: Qatar, Kuwait and United Arab Emirates. Since camels are the most likely zoonotic reservoir for MERS-CoV, we conducted a detailed epidemiological, clinical and genomic study to ascertain common exposure and transmission patterns of all cases of MERS reported from Hafr Al-Batin and relate it to other available genomic sequences from KSA and globally.

2. Methods

2.1. Selection of MERS-CoV cases

MERS-CoV cases reported from the Hafr Al-Batin were selected for study. Epidemiological, clinical and laboratory details were collected. Clinical information included demographic data, clinical symptoms and signs, co-morbidities, contact with animals and travel history

2.2. MERS-CoV testing and genomic analyses

All suspected cases meeting the basic MERS-CoV infection criteria are confirmed in Saudi Ministry of Health regional laboratories by reverse transcription, real-time-PCR as previously described.⁴ MERS-CoV genomic sequences were available from a subset of the Hafr Al-Batin MERS cases.¹⁰ These viral sequences were used to test possible transmission routes for the virus and establish the plausibility of epidemiologically suspected virus transmissions using a previously described statistical test of

transmission.⁴ Briefly, the expected number of sequence changes between two sequences was calculated as the product of the time interval between sampling, the evolutionary rate of the virus, and the maximum length of sequence shared by the two virus genomes. If the number of differences between two sequences accumulating in a given time is assumed to follow a Poisson distribution, with λ equal to the expected number of mutations, the probability of finding this number of differences between the two sequences by chance can be calculated from the cumulative density function of the Poisson distribution. A transmission pair was rejected if the number of observed mutations exceeded the 95% upper cumulative probability value. To reduce the chance of type 1 statistical errors due to multiple testing, a Bonferroni correction was applied to the significance cutoff, resulting in an adjusted significance level of $3.85 \times 10e-3$. The rate of evolution of MERS-CoV has been estimated at $1.12 \times 10e-3$ substitutions per site per year (95% credible interval [95% CI], $8.76 \times 10e-4$; $1.37 \times 10e-3$).¹⁰

In addition, a plausibility test was added. A reproductive time for MERS-CoV has been estimated at 7–12 days,¹¹ which represents the time from symptom onset in a primary case to symptom onset in a secondary case. This estimate is largely derived from hospital-based infections which may be dominated by patients with renal failure and other co-morbidities,^{4,12} as well as close contact with infected cases resulting in an underestimate of the generation time. For testing the global transmission of the virus, we included an asymptomatic period when a patient might still be infectious, estimating that a case remains infectious for 14 days, and assuming that identification would occur within 7 days of infection. Thus, any two cases might be plausibly directly linked if they meet the statistical sequence test and the two sample dates differ by 21 days or less. This calculation was used to assess the likelihood that virus transmission occurred directly between two test cases and was

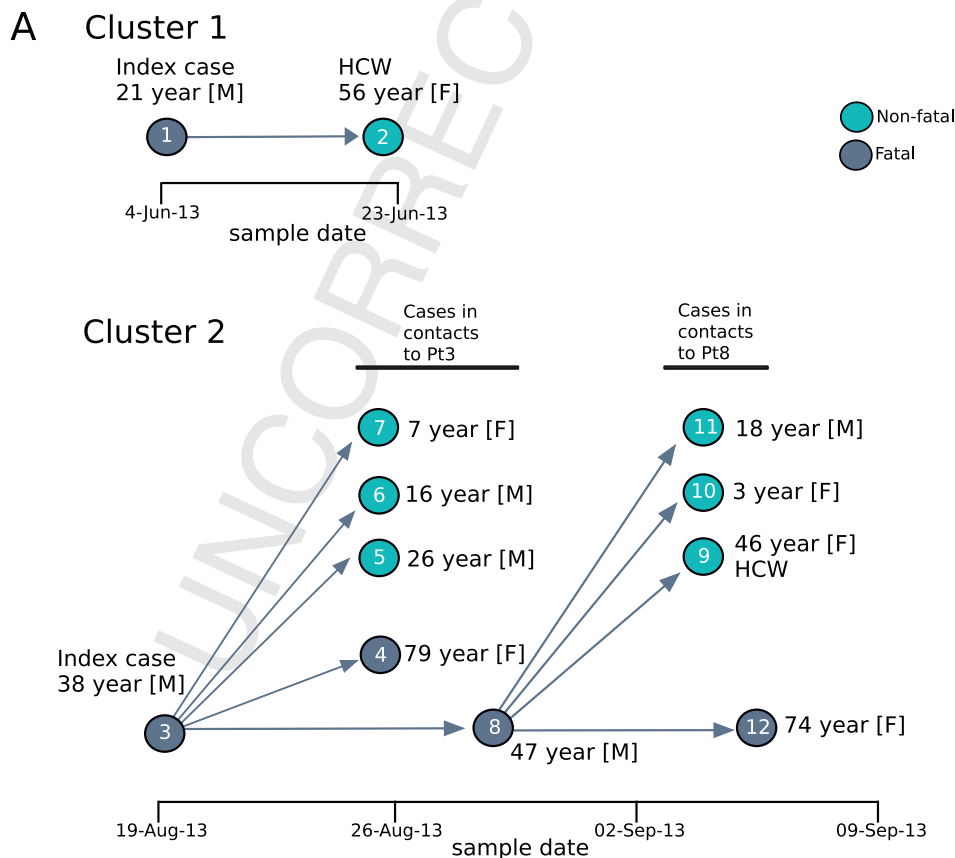


Figure 1. A Diagram is showing the transmission of the two clusters and the secondary transmission.

Table 1
shows symptomatic and asymptomatic cases and comorbid conditions.

Cases	Age	Gender	Comorbidity	Outcome	Animal Contact
Pt1 [†] Index case first cluster	21	M	none	died	yes
Pt2	56	F	none	alive	no
Pt3 [†]	38	M	DM	died	yes
Pt4 [†]	79	F	DM, HTN	died	no
Pt5	26	M	none	alive	yes
Pt6	16	M	none	alive	yes
Pt7	7	M	none	alive	no
Pt8 [†]	47	M	Obesity, DM, HTN, smoking, HD	died	yes
Pt9	46	F	DM, HTN	alive	no
Pt10	3	F	none	alive	no
Pt11	18	M	none	alive	no
Pt12 [†]	74	F	DM, HTN	died	no

[†] Symptomatic case; DM=Diabetes Mellitus,HTN= hypertension, HD= Hemodialysis; M = male; F= female.

applied to all cases infected with the Hafr-Al-Batin_1 MERS-CoV variant.

2.3. Statistical analysis

A descriptive analysis was used with comparison of percentage using P values as was considered to be significant if the P value was < 0.05.

3. Results

3.1. MERS-CoV cases and clusters

Between June 30, 2013 and August 31, 2013, there were 12 positive MERS-CoV cases in the Hafr Al-Batin area. Two index cases and two clusters were noted. In the first cluster, the index case was a 21 year-old non-Saudi shepherd with onset of symptoms in May 31, 2013 and a secondary case, a healthcare worker contact had who had an asymptomatic infection (Figure 1). The second cluster involved a 38 year-old Saudi male, owned and directly cared for camels, and had onset of symptoms in August 8, 2013. This patient infected five additional cases and one of the secondary contacts infected an additional four individuals (Figure 1).

3.2. Comorbidity and Clinical Presentations

Of the 12 cases, five (41.7%) had contacts with Camels. The first index (June 2013) case was a shepherd. In the two clusters, five patients died including the 2 index cases and 3 of their close contacts (four out of the five mortalities had comorbidities). Of those with comorbidities, all had diabetes mellitus, three had hypertension, and one was also obese and was a smoker. Comorbidities were present in four (80%) of the five symptomatic cases and in one (14%) of the seven asymptomatic cases (P = 0.07) (Table 1).

All symptomatic cases had fever, cough, shortness of breath and four (80%) complained of sore throat. Two (40%) had headache, one (20%) complained of hemoptysis and one (20%) had nausea (Table 2).

Table 2
Clinical Presentations among symptomatic cases.

Symptom	No. of cases	%
fever	5	100
sore throat	4	80
cough	5	100
shortness of breath	5	100
hemoptysis	1	20
nausea	1	20
headache	2	40

3.3. Contact Investigation

The contact investigation was carried out for both family contacts and healthcare worker contacts. Among the family contacts, 7 out of 36 (19.4%) tested positive and 1 of 51 (2%) healthcare worker contacts was positive for MERS-CoV (P = 0.0078).

3.4. Genetic tracing of MERS-CoV transmission and possible linkages

For the first Hafr Al-Batin cluster we obtained full MERS-CoV genome from the index patient 1 (Hafr-Al-Batin_1_2013), however no useful sequence could be obtained from the only positive contact in that cluster (Patient 2 a health care worker). For the second transmission cluster, genomic sequences were obtained from Patient 4 (Hafr-Al-Batin_5_20130), Patient 5, (Hafr-Al-Batin_4), Patient 8 (Hafr-Al-Batin_6) and Patient 12 (Hafr-Al-Batin_2). We were unable to obtain sequence from Patient 3, however an ancestral sequence for the entire family clade was reconstructed and used as a surrogate for the Patient 3 sequence. Possible transmission routes are indicated in Figure 1. Each patient is indicated by a filled circle placed by sample date, blue-filled circles indicate patients with sequence, grey-filled circles indicate cases with no available sequence and the orange-filled circle represents the reconstructed ancestral sequence.

Individual cases in the second Hafr Al-Batin transmission cluster were plotted by date of the sequenced sample (Figure 2). Blue-filled circles indicate cases with sequence data, the orange-filled circle for Patient 3 indicates that an ancestor sequence for the clade was reconstructed and used as a surrogate, grey-filled circles indicate cases with no available sequence. Some transmissions are statistically allowed including Patient 3 to Patient 8 and Patient 4, 5 or 8 to Patient 12 (green arrows). However, transmission from Patient 3 to Patient 4 or Patient 5 is not likely to have occurred (dashed red arrows); other sources of the infection should therefore be considered for Patient 4 and Patient 5.

To examine MERS-CoV sources on a broader scale, the possible transmissions amongst all patients known to have been infected with the Haf Al-Batin variant were tested (Figure 2, upper panel). The Hafr-Al-Batin_1 clade was first observed in Patient 1 (Hafr-Al-Batin_1) in May 2013¹³ and since then has been identified in 19 MERS patients¹⁰ and 1 camel⁸ in Riyadh, Hafr Al-Batin, Madinah, and Qatar.

We have depicted all cases by sample date and color-coded the circle by subclade (Figure 3 upper panel). All statistically supported transmissions are marked by arcs connecting the relevant patients. Several important patterns appear. Hafr-Al-Batin_1, Riyadh_8, Riyadh_12 are linked to a large number of possible pairs. Hafr-Al-Batin_1 is an early sequence in this clade may be representative of

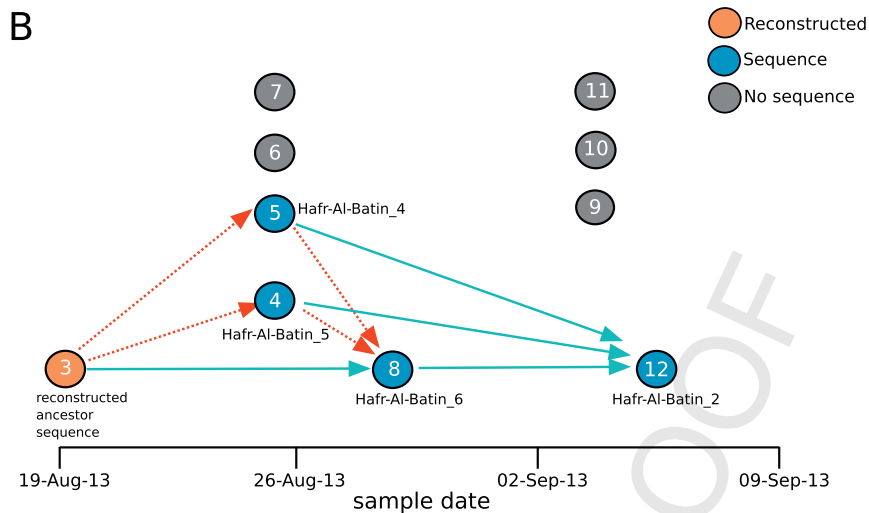


Figure 2. Transmission chains HAB Cluster2.

the camel to human zoonosis that gave rise to this clade, showing linkage to 10 of the 19 Hafr Al-Batin cases. The 4 linkages from Riyadh_8, 3 linkages from Riyadh_11 and 4 linkages from Riyadh_12 viruses may provide important clues. These are viruses from patients in Riyadh with no direct links to the Hafr Al-Batin region and no contact with animals, including camels. However, within a period of one month, similar viruses are observed in Riyadh, in the Hafr Al-Batin region as well as in Madinah, with statistical support for direct transmission events. Any MERS-CoV transmission model must account for this rapid virus movement. Furthermore, sequences from three viruses in the recently described camel/human transmission cluster in Qatar also fall within the Hafr Al-Batin cluster.^{4,8} The transmission testing supports the conclusion that the Qatar human and camel viruses are directly related to the Saudi Hafr Al-Batin cluster.

Adding the 21-day plausibility filter, the pattern is reduced in complexity; however important features remain (Figure 3, lower panel). The linkages between the Riyadh_12 patient and the patients in the Hafr Al-Batin family cluster (Hafr-Al-Batin_4, 5 and 6) remain. In searching for alternative sources of the infection of Patient 4 and 5, Riyadh_12 or the source of the infection of Riyadh_12 should be considered, including exposure to health care facilities, or health care workers, consumption or exposure to uncooked animal products, exposure to camels or other animals directly. A second network of transmissions passes the plausibility test with transmissions between the Riyadh_8, Riyadh_11 and Riyadh 17 cases and beyond to Madinah_1 and Madinah_3.

4. Discussion

In this report we describe the possible transmission dynamics of MERS-CoV in community case clusters from the Hafr Al-Batin region. A cluster was defined by WHO as the occurrence of > 2 patients with onset of symptoms within an incubation period of 14 days. The transmission occurs in the same setting such as a classroom, workplace, household, extended family, or hospital.¹⁴ Since the emergence of MERS-CoV, a number of clusters involving more than two people¹⁴ have been reported from France,^{15,16} Italy,¹⁷ Jordan,¹⁷ KSA,^{3,4,18} Tunisia,¹⁹ UAE,²⁰ and Qatar. The known 14 primary cases in these clusters were adult men.²¹ Of the involved individuals, 26% occurred in healthcare setting.²¹ The largest healthcare associated MERS-CoV cluster was reported from Al-Hasa, Saudi Arabia.⁴ In an earlier family cluster from Saudi Arabia, an adult male index case resided in an extended household of

10 other adults and 18 children. Secondary cases were identified in two sons, and a grandson.³ The findings from previous clusters showed that immunocompetent contacts exhibit mild symptoms.^{20,22} In the UK cluster of MERS-CoV, two cases of MERS-CoV infection were confirmed and one of the two cases had severe illness. None of the 59 healthcare workers contacts had infection.²⁰ In the Hafr Al-Batin cases reported here, 19.4% among the family contacts tested positive and 2% of the healthcare worker contacts was positive for MERS-CoV ($P = 0.0078$).

One of the differences between primary cases and secondary cases in MERS-CoV clusters is that primary cases usually acquire infection through contact with non-human sources of the virus.²³ The cluster showed the spectrum of illness of MERS-CoV from asymptomatic to a fulminant disease as observed previously.³ In the current study, animal contact was reported in 41.7% of all cases. The presence of animal contact among asymptomatic family contacts further complicate the issue of having secondary cases as a result of direct contact or the result of exposure to the same source or host of MERS-CoV. In fact, for family cluster 2, our genetic data indicate that while patient 8 is likely to have acquired the infection from the index patient 3, at least two of the infected contacts (patients 4 and 5) could not have been directly infected from patient 3 and alternate source should be considered.

Although, there were transmissions within healthcare setting and interfamilial, the number of transmissions seem to be limited. This finding is similar to previous observations from known clusters^{4,24,25} and that secondary attack rates among family members of patients in other clusters appear to be low.^{3,4,17,25,26} In a recent large screening study, family contacts had a higher positivity rate (3.6%) than HCW contacts (1.12%).²⁷ Systematic implementation of infection prevention and control measures in reported clusters involving healthcare settings has appeared to limit onward transmission to HCW and hospitalized patients.^{4,15,20,25,28,29}

A large annual camel fair takes place in Hafr Al-Batin each November–December to March with movement of a large number of camels both to and from Hafr Al-Batin.⁹ It seems that the timing of the Hafr Al-Batin sequence divergence is consistent with the annual fair and animal movement. It remains unclear if primary cases had acquired MERS-CoV from direct animal contact or as a result of contact or consumption of animal products, unpasteurized camel milk and products (ice cream). It seems that camels appear likely as source but other animals have not been ruled out and that the quantity of sequence data from camels has not been overwhelming. More detailed case control studies with detailed

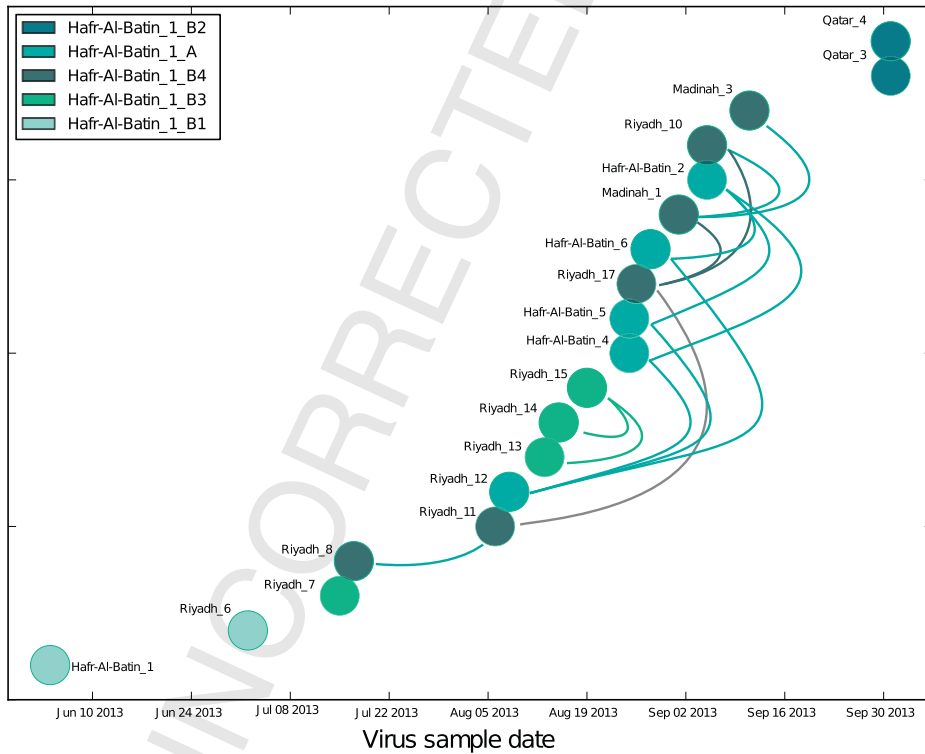
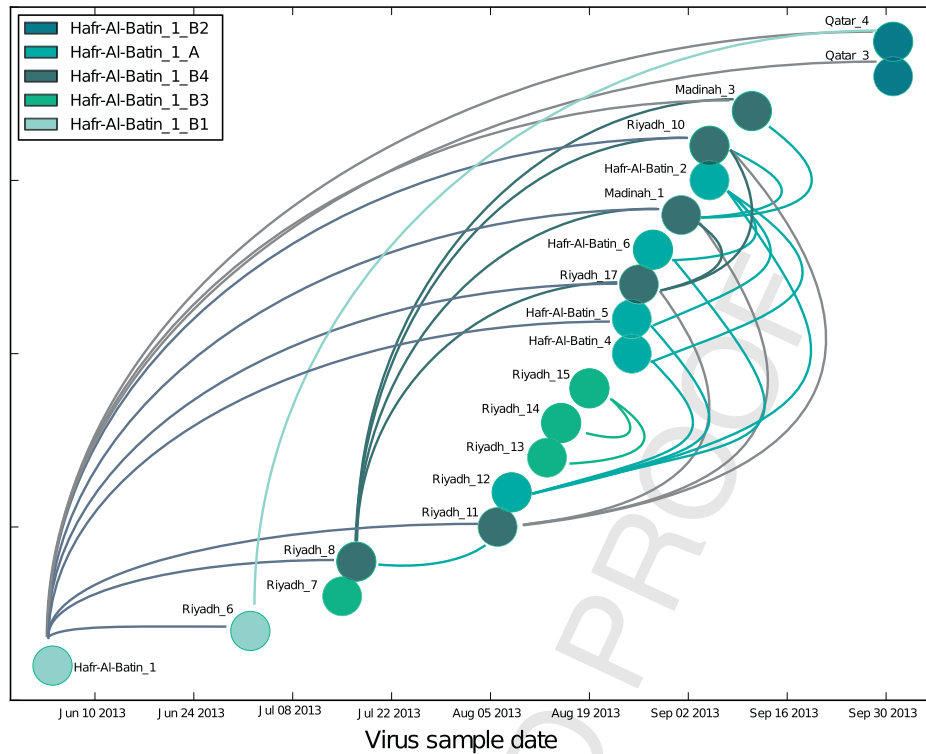


Figure 3. Cluster timeline HAB All and 21 day limit.

case histories, epidemiological information and genomic analysis are being conducted to delineate the missing pieces in the transmission dynamics of MERS-CoV outbreak.

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